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ADDRESS OF THE PRESIDENT*

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FOR the subject of my address I have chosen "Medicine in the Changing Social Order." History is the record of constant political, economic, scientific, and social change. When the forces of construction prevail, like human welfare, political liberty, scientific research, economic freedom, and preservation of public health, the social structure is strong. When the forces of destruction prevail, such as war, pestilence or tyranny, human liberty is curtailed, industry wanes, science languishes, human health is in jeopardy and the social order is prostrated. One of the most perplexing problems before society today is the unsettled status of the medical profession in the social structure and the consequent effect upon the health of the people.

Public welfare demands that all levels of society receive adequate medical care, for it is not a luxury but a necessity to every community as well as to every individual. Not all of them are getting it. They should have it. But how? Physicians have contributed millions of dollars every year in medical service to the poor and underprivileged, but it is not enough. It is an obligation of the public and should be provided by taxes or insurance wherever private funds are unavailable.

These questions are not new, nor have they suddenly arisen to bedevil us. The challenge for social change usually arises out of injustice or oppression of some class of society. Such a challenge, although not the first, had its roots in the philosophy of Karl Marx and the rise of

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socialism. When Bismarck became alarmed at the rapid progress of socialism, in the early eighties of the last century, and when he found that he could not stem the tide by coercion or suppression, he decided to throw a sop to the socialists in the form of sickness and accident insurance, together with old age pensions, all of which were adopted within the decade. When he submitted the bills to the Reichstag he said: "Do this without fearing either sacrifice or the cry of state socialism for I believe the socialists will then sound their bird cry in vain." He predicted that the sop would silence the socialistic clamor and stop its advance. He was a poor prophet. Socialism kept on growing in Germany and spread rapidly to the following countries: Austria, 1883; Hungary, 1891; Finland, 1895; Great Britain, 1897; Denmark, France and Italy, 1898; Spain, New Zealand, British Columbia, 1902; Russia and Belgium, 1903; State of Nuevo, Mexico, 1906; Transvaal, 1907; Alberta, Bulgaria, Newfoundland, and the U. S. A. (for federal employees), 1908; Quebec, 1909; Nova Scotia, Manitoba, 1910; Switzerland and Peru, 1911; Rumania, 1912, and 45 of the states of the United States, 1911 to 1918. Within thirty years the proposed so-called socialistic proposals literally swept the world. One cannot say that such a tide of opinion is only passing agitation, nor can such a mass movement be retarded by merely asserting that it is wrong. While extreme radicalism seldom forces its own program successfully, it often does succeed in liberalizing conservative thought, so much so, indeed, that what seemed radical yesterday, becomes only liberal today and tomorrow may be looked upon as conservative. Perhaps we as a profession can derive some profit by these lessons of history, which illustrate the influence of changing social attitudes upon the problems of community health.

The United States took the first step toward social health insurance when it was adopted for federal employees only. The next step came with the adoption of workmen's compensation laws by forty-five of the states. It is with some chagrin that we must admit that the medical profession had little voice in their formulation and enactment. Employers, labor leaders, and lawyers were its principal proponents due, it was accused, to the truculent attitude of the medical profession.

It is not my purpose to discuss the merit or lack of worth of the many plans and schemes proposed but rather to consider the philosophy or lack of philosophy of organized medicine in meeting the issues. Twenty years ago I became rather concerned about the apparent indifference of the profession toward what seemed very radical trends and expressed the fear that unless we familiarized ourselves with them so that we could take an intelligent part in the discussions and decisions of the problems, others would decide them without us and in a way that might be unfair to the public and to us. After two decades I have the same fear. Now, as then, I am apprehensive that we may not be sufficiently social-minded to cooperate with other groups in meeting the issues. Medicine certainly cannot attain its proper place in society by resisting all of the impacts of social change.

Twenty years ago it appeared that the next step would be health insurance, compulsory or voluntary. However, even after two decades, the debate continues, but there seems to be increasing doubt concerning

the feasibility or the advisability of adopting compulsory health insurance. On the other hand, nearly everyone favors voluntary insurance. However, there is still much conflict of opinion as to the various proposed plans; how they may be carried and administered and the basis of equitable costs. The costs of life, accident, and indemnity insurance are determined by actuaries after experience with hundreds of thousands of cases and with such scientific accuracy that there is no doubt about the just premium to be charged. There is very little actuarial experience with any of the plans for health insurance, although some of them were tried on a small scale many years ago. Whether they can be carried for a dollar a month or ten dollars can only be learned by experience, just as the life insurance companies had to learn by actuarial determination. But it can be done by experimentation with health insurance. Health insurance is no exception to the old saw: "There are two sides to every question." You are too familiar with the opposing arguments to justify detailed discussion here.

The feature about these problems that bother me is not the difference of opinion, or that the questions have not been quickly answered, but the too often heard criticism of the medical profession, whether deserved or not. I fear some of it is deserved. It does seem to be opposed to any change in its social status or any alteration of its age-old privileges. No doubt, the public has lost some degree of confidence in the medical profession. I cannot escape the belief that we will serve the public best by increased social-mindedness, less pugnacity, a thorough understanding of the social significance of the problems involved, so that we may take an intelligent, calm, judicial, and sympathetic part in deciding the issues at hand. The fear of social change is well illustrated by the acrimonious debate engendered when the national health insurance bill was introduced into the House of Commons in 1911. The British Medical Association had no voice in its formulation and opposed it bitterly, but Premier Lloyd George forced its passage. However, the experiment was less detrimental to the practice of medicine than anticipated. After the act had been in force seven years, a committee of the British Medical Association made the following surprising report: "The degree of unanimity so far disclosed is somewhat remarkable and suggests that the scheme, which is proving a distinct gain to the medical profession as well as to the public, be still further extended to the dependents of insured persons and for providing, when necessary, specialists, nursing service, hospital treatment, and maternity attendance."

Here we see a very radical medical social change, which by experimentation proved to have at least some merit. Medical social change now has become merely liberal legislation. Not all experiments will prove so salutary, some of them will fail. That lesson will be valuable too.

We cannot afford to have the impression grow that the profession is opposed to every social change. Perhaps we have exhibited too much combativeness and not enough of calm deliberation. It is possible too that the clever sarcasm, high-pitched invective, and evident rage of some

of the medical press may not be conducive to dispassionate reasoning when there are primary differences of opinion and approach.

Many plans and schemes have been proposed, some of them apparently feasible and fair, others impractical, many of them savoring of state medicine and some frankly socialistic. Several groups of society are sincerely interested in the solution and honestly believe that they alone have the final answer and look askance at the propositions of all other groups. Health departments inevitably think first of prevention. The physician is likely to think in terms of the private patient, always within the limits of his long cherished rights of individualism and professional freedom. He is impatient with the idea of mass approach, and statistical surveys. The social worker and his statistician are sure their figures answer all questions and solve all problems. The economist is equally sure he can furnish the solution. The sick man doesn't care so long as he gets well—for nothing. All of these group opinions, reached by way of a different approach, lead to divergent views and the solution is not yet. "When doctors disagree, who shall decide?" We all believe in the virtue of the democratic way of composing conflicting opinions by public and unhampered discussion, but it is sometimes difficult to restrain our impatience at the seemingly interminable delays. However, when we recall the inherent complexities of health problems, plus their increasing social aspects, perhaps we should give more sober consideration to the honest views of all concerned. First of all, we must concede that all groups, physicians, health departments, social workers, representatives of government, and the public, are honestly desirous of obtaining, in the American way, greater health security for all of the people without the surrender, by any group, of its freedom and above all, without political, governmental overlordship. Each group has some service of value to contribute. Clear thinking, calm deliberation, sympathetic discussion and lack of emotionalism are likely to lead to action and answers to some of the problems. Other answers may also be found if the fear of experimentation can be overcome.

The settlement of all problems cannot be obtained "out of hand." Some may be composed by cool, dispassionate, judicial discussion among the groups. Others may be tranquillized only by experimentation. The ideas of health insurance are too broad and intricate to be answered dogmatically by its proponents or its antagonists. After all, the health of the whole people is the paramount consideration. The upper income group of the population can secure as good medical care as they are willing to pay for. The indigent group gets reasonable care through tax funds. The near indigent and low income groups present the only real serious problem. The interested groups, public health agencies, physicians, social workers, and economists, all have wrestled with the diverse problems for more than two decades and the end is not in view. It would seem reasonable to expect that a working agreement upon general principles could have been agreed upon long ago.

For purposes of this discussion we are not particularly concerned with the other groups, but we should be much concerned with our own attitudes. "Self analysis is good for the soul." We may well ask ourselves whether we are giving "all-out" service to the solving of the

problems. Is the impression correct that the medical profession is constantly antagonistic or at least negative in its attitude? Is the profession in a state of social or unsocial torpor? Are these questions going to be answered without the cooperation of the profession, as were the workmen's compensation laws? Shall we permit a constructive health program for all the people to be formulated without our participation? We, of a so-called learned profession, may think much, perhaps overmuch, of our professional liberty. We shall fail in our full duty if we forget that ours is a profession; not a business, not a trade, but a calling, which implies public service. The public is so vitally interested in the practice of medicine that it looks upon it almost as a public utility. Hence, the public must be taken into our confidence and sympathetic consideration; otherwise we may be compelled to submit, as have the utilities companies, to public control. There ought to be a common ground upon which the saner elements of society could meet and make common cause with the profession so that justice might be done to the public and to the physician.

Organizations in the interest of groups have an increasing importance in the society of today; manufacturer and merchants' associations, farmers' leagues, labor unions, consumers' cooperatives, and societies of the learned professions now all act through organizations, the members of which often have more intense loyalties to their particular organization than to their political party or even patriotism to the country. Many of them date back to the medieval craft guilds like the guild of barber-surgeons, the forerunner of modern medical societies. In these, special privileges were established in the middle ages and added to from time to time by custom, tradition, and law. These privileges were granted by society, not as a right, but as a trust, because each one could perform some service to society better than others. Physicians were granted the special privileges of self-government, authority to control admission to membership and discipline; and adoption of rules of conduct (ethics) because members of their organization, only, could be entrusted to deal with health, life, and death and because to perform these duties a broad education, special preparation, and skill were required. Such privileges, accorded by society, impose obligation upon the recipient of giving back to society forever the service for which they were bestowed. If the organization forgets its ideals and descends to the level of self-interest, it endangers its liberty of action in society.

If our profession shows wisdom in adjusting itself to social changes by loyalty to the general welfare of the people and freedom from selfish professional interests, it will surely retain its cherished historic liberties. Otherwise society may withdraw the privilege. Privileges are too often looked upon as inalienable rights: Industry presumes to dictate wages and labor conditions, labor assumes the right to sit down and capture a plant or maim the "scab" and both labor and capital can assume the attitude of "the public be damned" or the medical profession can say: "Avaunt with all your social changes—we will practice medicine as we please, as we have always done." Privileged organizations must realize that the days of "the public be damned" are gone. The

medical profession rightly and jealously guards its professional liberty even to the extreme of being accused and convicted of conspiracy against the public. The medical profession is probably more closely knit and possessed of more power than any other professional group. It is given high privilege because of its healing objectives, its background of higher general education, its necessary special preparation and its code of conduct. The thinking public knows of its high ideals, that it is a group that can and does make science serve the noble art of healing and assuaging suffering. Gratitude usually surrounds the individual physician with an aura which gives to his profession the unique privileges which really place it in a perilous position; for such a gift demands great responsibility and requires great leadership lest it fail to fulfill its sacred trust. The profession has magnificently discharged its obligations to society from the professional standpoint by lowering the general death rate, by decreasing, eliminating, or bringing under reasonable control many dread diseases like tuberculosis, yellow fever, typhoid fever, diphtheria, malaria, pernicious anemia, and very many other diseases. The perils of childbirth to both mother and baby have been reduced 40 per cent and the deaths from infant diseases quite as much. The discovery of the vitamins and endocrines gives a new outlook and hope to suffering humanity. In this developing scientific age, science has been made to serve the sick so that we now dare to speak of scientific medicine. But all of these great accomplishments do not give to organized medicine the right to arrogate to itself the final decision of all questions pertaining to public health, whether medical, economic, sociologic, or questions of sound public policy. Do we, as a profession, sufficiently appreciate that the architecture of the social structure is changing and that there are other quite as necessary building materials as medicine? Unhampered individualism is passing, "believe it or not." Youth, our successors, will not be living in an age like ours, nor meeting the same problems and conditions that we did. "It is a new world." They will find that to master medicine and its allied sciences is not sufficient. In the practice of medicine, sociology has grown to great importance; indeed, medicine itself has become a social science; therefore it cannot possibly escape the impacts of changing social attitudes which will confront the younger generation of physicians with increasing force and will require of them to possess a much greater social consciousness than we have ever had.

Unfortunately, medical students have little or no preparation in the social sciences, such as history, political science, sociology, or economics, which are so necessary for social understanding and training for citizenship; and, as I see it, particularly for entering the practice of medicine which, in the future, will have an ever increasing and profound social significance. We want our intellectual medical progeny to cling to the splendid traditions of the profession, while becoming less class-conscious and individualistic, but at the same time more open-minded and aware of the interested concern of the public in matters of health. This new generation has been well trained and inspired by the best teachers to high ideals of service and research, so we need have

no anxiety about their progress in medicine and its allied sciences. Neither need we be solicitous about their ethics, the philosophy of morals, for after all, ethics is merely doing the right thing by one's patient, colleagues, and the public. But I confess that I still have some apprehension as to their social consciousness, for I am not sure that the most individualistic of the learned professions has left them a great legacy of social understanding.

Medical teachers allied with scientists insure the progress of medicine. The need is for its application to all the people. That is the great ideal. We hope it is not too far in the future. To accomplish it great leadership must take command. In the past there have been too many politicians and not enough diplomats. When the people are convinced that they are wisely led by medical statesmen and that the profession itself is imbued with unselfish, practically applied ideals and is inspired by lofty social understanding, mankind will reverently and with deep gratitude gladly accord to the medical profession all of the intrinsic values of its traditional professional liberty.

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PROLIFERATIVE CHANGES IN THE SENILE ENDOMETRIUM*

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THE traditional concept of the senile endometrium is of a mucosa which, having been deprived of its estrogen maintenance, has become thin and atrophic, with sparse, shrunken, and sometimes cystic glands, and with a scant fibrotic stroma. A number of authors in recent years have called attention to the fact that this is by no means always the case, and these observations have appeared to fit in with the now well-established fact that estrogen may be found in the urine of women long after the menopause or after castration.

The production of estrogen during the postmenopausal epoch would seem to explain the occurrence of proliferative endometrial pictures of one degree or another, especially since it is well known that the postmenopausal endometrium, unlike the postmenopausal ovary, is capable of reactivation by means of hormone stimulation. For this there is abundant evidence, both experimental (Clauberg, Kaufmann, Loeser) and clinical. The administration of adequate amounts of estrogen even to castrated women will produce a typical hyperplasia. For that matter, even a typical secretory endometrium can be produced in such women by the sequential injection of estrogen and progesterone. As an extreme example, Hübscher was able, by means of estrogen and progesterone, to reproduce a progestational histologic cycle in a woman of 80 years. From a clinical standpoint, the endometrial responses brought about in postmenopausal women by the functioning feminizing tumors of the granulosa-cell and thecoma groups constitute good illustrations of the responsiveness of the senile endometrium to the ovarian hormones.

By contrast, the evidence indicates that the ovary, once it has reached the end of its life span at the menopause, is not capable of re-activation by any means of hormonal stimulation. Only Westmann has reported contrary results in one case, but his observations have apparently been quite effectively refuted by the work of Tschertok and Penkow, Waldeyer, and others.

As to the source of the postmenopausal estrogen, there is as yet no certainty. There are still many who believe that such estrogenic sex sterols may be chemical metabolites of certain body sterols, with cholesterol as the probable mother substance. The fact that estrogens have been shown to be produced in other endocrine glands than the ovary, especially in the adrenal cortex, has led to the growing view that some such extraovarian endocrine gland source is responsible. The finding of estrogen long after complete removal of the ovaries, as well as

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the histologic study of senile ovaries, would seem to exclude the latter from consideration as sources of postmenopausal estrogen.

The present study, however, has to deal with the histologic rather than the hormonal aspects of this problem. In a previous paper (1936) from this laboratory (Novak and Yui) in which no less than 804 cases of hyperplasia were studied, 40 were found to have occurred beyond the menopause. In 1932 Taylor had also described the occurrence of hyperplasia postmenopausally. In both of these papers, however, as well as in the more recent paper of Taylor and Millen, these findings constituted a by-product in the study of the broader problems of adenocarcinoma or postmenopausal bleeding.

Perhaps the most direct study of the endometrium in a large group of cases of postmenopausal bleeding is that of Breipohl (1935), whose material consisted of 130 postmenopausal endometriums from women over forty-five years of age and at least six months after the last menstruation. In 76 of these, the mucosa was atrophic, including in this group 11 in which practically no tissue was removed, and 4 in which it was described as necrotic. Adenocarcinoma was found in 22 cases while in fully 31 cases there was evidence of proliferative activity. This latter group embraced 15 cases of hyperplasia (including 2 with granulosa cell carcinoma of the ovary), 11 in which the endometrium was described as corresponding to a proliferative phase, and 3 in which secretory endometrium was found. This last-named group must be viewed with skepticism as applied to the senile endometrium, because of the fact that Breipohl included in his study patients in whom the menopause had occurred only six months previously. There is no doubt that menstruation and ovulation may occur after much longer intervals than this. Unfortunately he gives details of only one of these three patients, and in this the interval after the last menstruation was only one year, the patient being fifty years of age. He emphasizes, however. that more than one year had elapsed since the menopause in 26 of the entire proliferative group of 31, and in 9 more than ten years had elapsed.

Closely related to this question of postmenopausal hyperplasia in the case of women with grossly normal pelvic organs is that of the endometrial changes and the endometrial bleeding which have been described in association with various tumors of the ovary. The role of the estrogen-producing tumors (granulosa cell carcinoma and thecoma) in this connection is now universally accepted, and needs no elaboration here. Much less clearly explained is the uterine bleeding which occurs in a small proportion of ovarian tumors of other types, such as carcinoma, fibroma, cystadenoma, and Brenner tumors. Studies on this question have been made by a good many authors (Schiffman, Lahm, Meyer, Moulonguet-Doléris, Wehse). Some, like Schiffman, described hyperplasia of the endometrium in association with various tumors, to which they were inclined to ascribe a hormone-producing effect, although such tumors are not commonly accepted as having any such effect. The relative frequency of postmenopausal hyperplasia in the absence of any tumor would seem to cast doubt on such an assumption, and to favor the view that such ovarian tumors and hyperplasia might co-exist without any relation of cause and effect.

Other hypotheses, none very satisfying, have been suggested to explain the bleeding seen in association with some cases of the nonspecific types of ovarian tumors. Moulonguet-Doléris, for example, believed it to be due to a trophic effect on the endometrium resulting from the effects of the tumor on the ovarian nerve plexus, while Wehse suggested as the responsible factor the ovarian metabolic changes induced by the growth. Tietze ascribes the important role to the metabolic and vascular changes produced by the tumor, while Meyer stresses the possible role in at least some cases of a co-existing or incorrectly interpreted functioning neoplasm.

Our own opinion, based on the study of a good many cases, is that ovarian tumors, with the exception of those known to have definite endocrine-producing function, have no characteristic effect on the endometrium. Since, however, there is some difference of opinion on this point, we have excluded such cases from our material with the exception of one or two cases mentioned below, which illustrated certain points and in which it was reasonably certain that no noteworthy effect on the endometrium could be produced by the tumor.

Our present study is based on the microscopic examination of 137 postmenopausal endometriums obtained either by curetting or hysterectomy. No especial selectiveness was exercised, except to eliminate those cases in which the material was too scanty to permit of histologic conclusions and those in which there were associated lesions, more particularly ovarian tumors, in which a modification of endometrial histology by the lesion was at least theoretically possible. On the other hand, a number of cases are included in which simple inactive ovarian lesions, such as germinal inclusion cysts or retrogressed endometrial cysts, were present. Moreover, in a good many cases uterine lesions, such as small or moderate myomas, were present, as it is difficult to believe that they would exert any important effect on the endometrium. Finally, in 10 cases carcinoma of the cervix was an associated lesion, while cervical polyps were present in four. These conditions were assumed to be the cause of any bleeding which was noted in the clinical review of the cases in our series.

The elimination of cases in which curetting has yielded such scant tissue that satisfactory histologic examination was impossible should be stressed, because there is no doubt that many if not all of these represented extreme atrophy of the endometrium. In Breipohl's study this assumption was actually made, but it did not impress us as fully warranted. This point obviously has a bearing on the incidence of the atrophic type of endometrium in our series, as something like 20 cases were eliminated from the series on this account. No case is included in which there was an interval of less than two years between the last menstrual period and the time of operation.

It is a well-known fact that ovarian activity, as indicated either by irregular normal ovulatory cycles or by persistence of hyperplasia and other lesser degrees of growth activity, may continue for a considerable

time after the last menstrual flow. Rarely, however, would one expect evidence of this functional ovarian persistence for much over a year, so that the two-year limit which was arbitrarily chosen for our series seemed like a fair one as indicative of the postmenopausal status. Moreover, the majority of our cases, as will appear below, were women in whom the

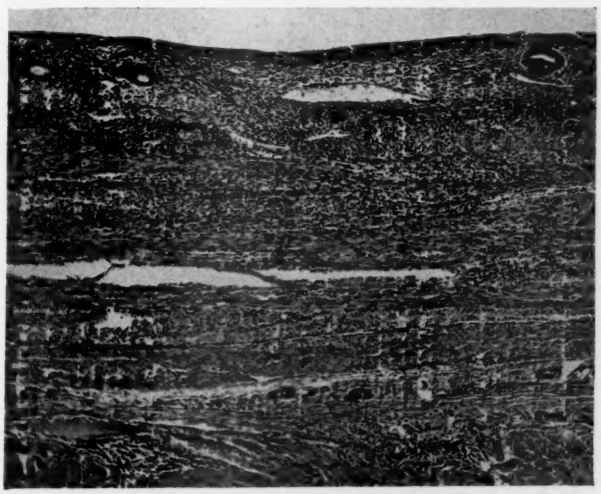

Fig. 1.—Atrophic endometrium four years after menopause, in patient of 52 years.

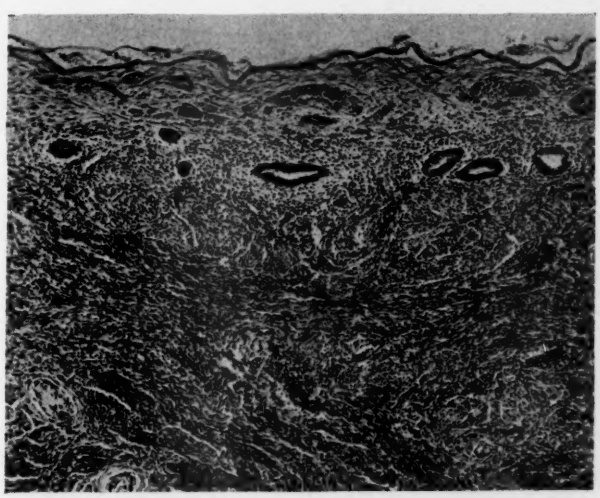

Fig. 2.—Atrophic endometrium nine years after menopause, in patient of 58 years.

postmenopausal span was much longer than two years. In only a fraction of our cases were the ovaries available for study. We are presenting no detailed report of the ovarian findings, but, suffice it to say, no histologic evidence could be obtained to indicate any persistence of ovarian function long after the menopause. This would not apply to ovaries removed within a year or two after the menopause. As a rule,

however, the ovaries presented the characteristics commonly attributed to the senile ovary. This is in conformity with the results obtained by Novak and Yui in the examination of 26 ovaries from cases of postmenopausal hyperplasia. These negative histologic findings do not exclude the possibility of postmenopausal production of estrogen by some ovarian element, but they make it seem unlikely.

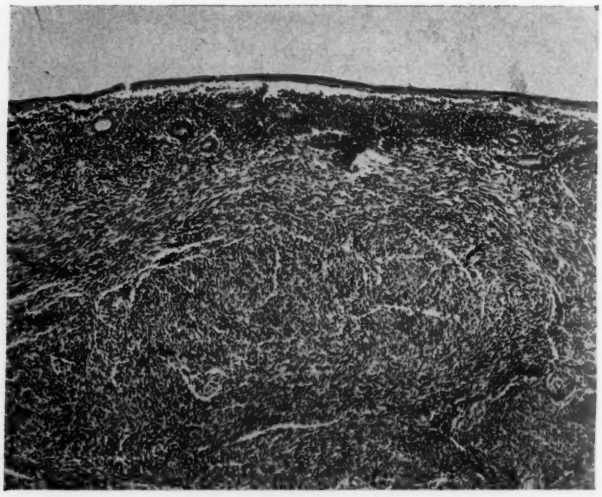

Fig. 3.—Atrophic endometrium six years after menopause, in patient of 55 years.

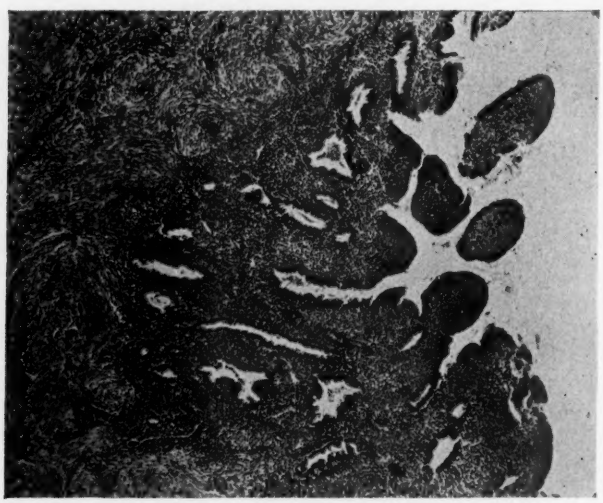

Fig. 4.—Moderately proliferative endometrium twenty-four years after menopause, in patient of 61 years.

At the outset it may be stated that the traditional concept of the senile endometrium as a very atrophic tissue was borne out in less than half of our cases, 62 out of 137. On the other hand, in a substantial proportion, varying degrees of proliferative activity were observed. The

most sensible plan of grouping the cases histologically appeared to be the following:

1. The thin atrophic mucosa, in which the surface and gland epithelium is either of normal height and appearance or flattened, the stroma more or less fibrotic, and the glands sparse and not infrequently cystic (Figs. 1, 2, and 3).

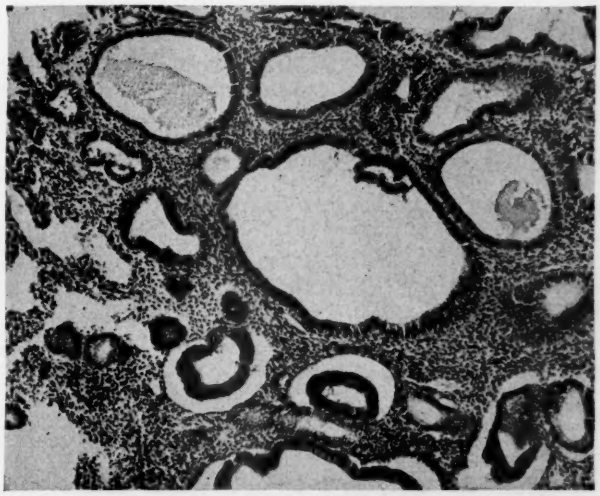

Fig. 5.—Typical Swiss cheese hyperplasia ten years after menopause, in patient of 50 years.

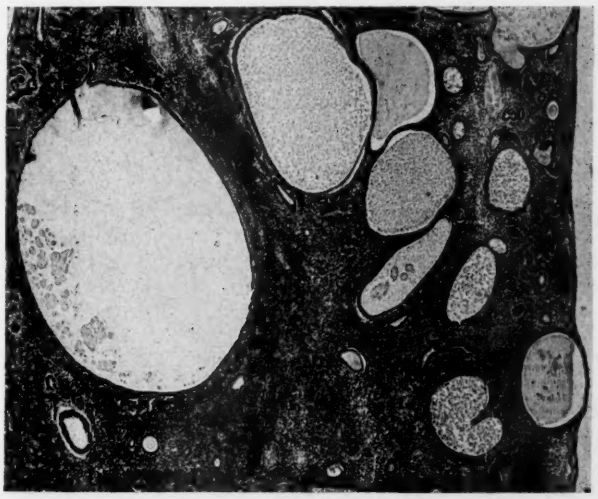

Fig. 6.—Active hyperplasia twenty-one years after menopause, in patient of seventy-one years.

2. Moderately proliferative pictures like those seen during reproductive life in the follicular (postmenstrual or early interval) phase of the cycle (Fig. 4).

3. Outspoken and apparently active hyperplasia identical with the hyperplasia of the reproductive phase of life, and characterized by the

Swiss cheese gland pattern, an intact epithelium with often dark-staining nuclei, and an abundant compact stroma (Figs. 5 and 6).

While the above three groups were those originally outlined for our review, we soon found that a fourth and well-defined type of endometrium kept recurring very frequently. To this we have applied the designation of

4. Retrogressive hyperplasia. In this the Swiss cheese pattern is perfectly marked, but the inactivity and retrogressiveness of the process is indicated by the fact that the epithelium is often low and atrophic, and the stroma obviously fibrous and inactive, so that with the ordinary hematoxylin-eosin stain the stromal fields stain pink instead of the

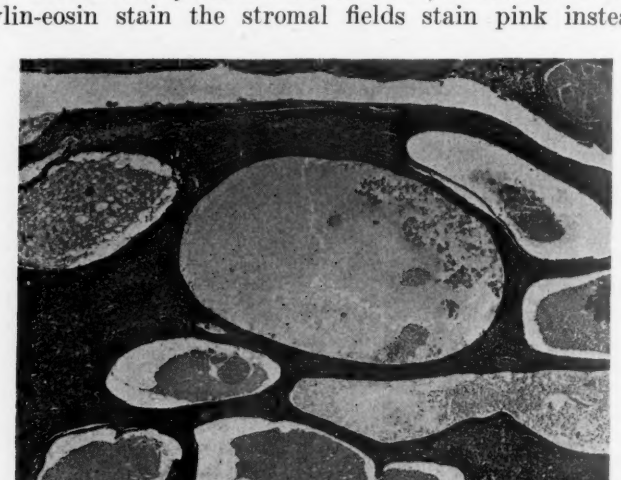

Fig. 7.—Retrogressed hyperplasia ten years after menopause, in patient of 51 years. Note flat epithelium and fibrous stroma.

dominant blue of the active hyperplasia. In passing it may be added that the fibrotic appearance of the stroma appears a more reliable indicator of hormonal inactivity than does the epithelium, which may remain tall and active-looking for many years after the menopause, even when the stroma is very fibrotic (Fig. 7).

THE HISTOLOGIC PATTERN IN DIFFERENT AGE GROUPS

It seemed advisable, if we were to study the postmenopausal history of the endometrium, to divide our cases into age groups, in order to determine whether any particular pattern can be correlated with any age subdivision. It was quite obvious, as will appear below, that this is not the case, and that the most conspicuous finding on such a correlative study is the hopeless disparity of the findings in this respect. In some women the endometrium is extremely atrophic within a year, sometimes only a few months after the last menstrual period, while in others the mucosa of women thirty or forty years after the menopause may be the seat of an active hyperplastic process indistinguishable from that seen so often during reproductive life.

Of our 137 cases 63 were from two to five years (inclusive) beyond the menopause. The endometrium in 28 of these was atrophic, while in 10 it showed a moderate proliferative picture, in 11 hyperplasia, and in 14 a retrogressed hyperplasia. The ages of these patients varied from 39 to 60 years.

Fig. 8.—Typical active hyperplasia forty years after menopause, in patient of 87 years.

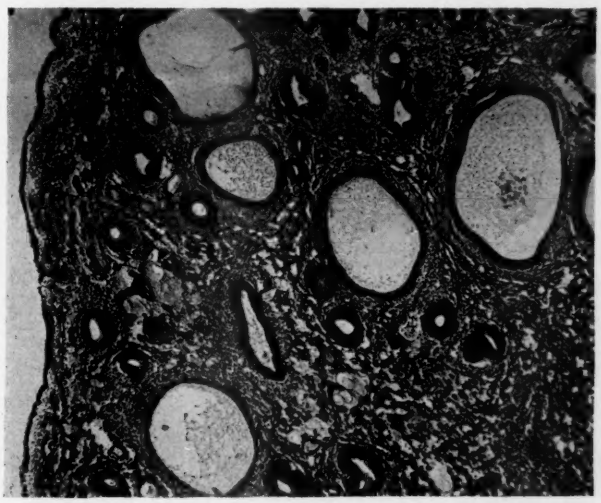

Fig. 9.—Active Swiss cheese hyperplasia thirty years after menopause, in patient of 80 years. See high power of mitoses in epithelium (Fig. 10).

In the group of 31 cases from five to ten years postmenopausal, the endometriums were classed as atrophic in 13, moderately proliferative in none, hyperplastic in 7, while the remaining 11 showed retrogressed hyperplasia. The ages of the patients in this group varied from 45 to 65 years.

The group of 17 cases from ten to fifteen years after the menopause embraced 10 atrophic endometriums, none with moderate proliferation, 1 with hyperplasia, and 6 with retrogressive hyperplasia. In this group the age variation was 56 to 67 years.

Finally, there was a group of 26 patients in whom the menopause had occurred more than fifteen years previously, including 2 in whom 40 years had elapsed since the last menstruation (ages 80 and 87). Only 11 of this group showed typical atrophy, while 4 showed moderate proliferation, 9 definite hyperplasia, and 2 retrogressed hyperplasia. The most remarkable group was that showing hyperplasia, and it is of interest to note that this occurred with especial frequency in the oldest members of this group (Figs. 8 and 9). The ages of these 9 patients were 87, 80, 73, 71, 70, 66, 62 (2 cases), and 50. On the other hand, the youngest member of this group, a patient of 49 years who had had a premature menopause sixteen years previously, showed a marked endometrial atrophy.

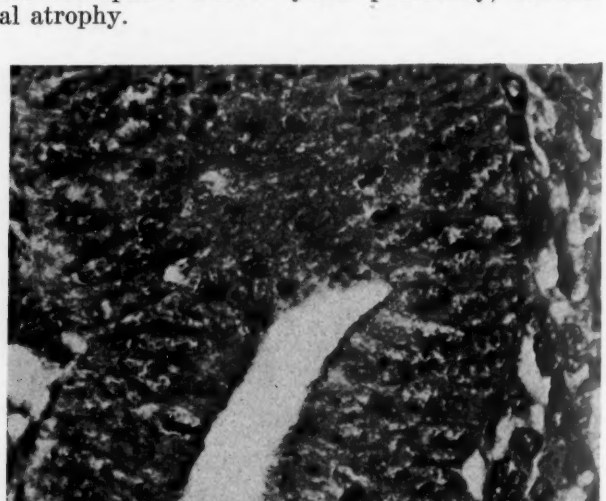

Fig. 10.—High power picture of another area in case shown in Fig. 9. Note mitoses and stratification in epithelium.

Adding these groups together, it is seen that the classification of the endometriums in the entire series of 137 postmenopausal cases is as follows: atrophic 62, moderate proliferation 14, hyperplasia 28, and retrogressed hyperplasia 33. Fully 42 (28.3 per cent) endometriums, therefore, embracing the moderately proliferative and hyperplastic groups, showed a degree of proliferative activity comparable to that seen during the reproductive epoch, while those in whom there was evidence of active hyperplasia comprised 28 (19.2 per cent). In the majority of these cases, however, the hyperplasia was not uniform throughout the sections which were available to us for study. In those in whom hysterectomy had been done, and in whom blocks of the uterine wall were available, it was often seen that the hyperplasia occurred in large patches in an endometrium which otherwise showed only slight proliferation or even atrophy, and in some cases there was a tendency to polyp formation. We feel sure, however, that anyone examining

these sections would agree that the hyperplastic areas were indistinguishable from those seen during reproductive life. In a number the activity of the hyperplastic process was further indicated by the finding of mitoses in the epithelium or stroma, more often the former (Fig. 10).

CLINICAL BEARING

The only clinical symptom which one would think of in relation to postmenopausal endometrial proliferation is bleeding. As regards the atrophic group, suffice it to say that bleeding was a symptom in 29 of the 62 cases of this type (7 cases of cervical carcinoma and 1 of cervical polyp eliminated), and in most of these it constituted the indication for diagnostic curettage. In practically every one, however, the bleeding was of very scant or spotting character, the duration varying between two days and two years. In other words it represented the type of postmenopausal bleeding which we characteristically associate with so-called senile endometritis. In many of our cases evidences of inflammatory infiltration were evident on microscopic examination. The bleeding in such cases probably has its source in tiny superficial areas of the atrophic endometrium, similar to those which can be visually demonstrated in senile vaginitis.

No such explanation would seem applicable to the proliferative group, and yet many cases of this group were characterized by bleeding. No less than 10 of the 14 moderately proliferative group (1 case of cervical carcinoma and 1 of cervical polyp eliminated), and no less than 12 of the 28 cases in the hyperplasia group (eliminating 1 case of cervical carcinoma and 2 of cervical polyp) were characterized by bleeding, in some cases slight, in others fairly free and sometimes of rather long duration. Since no other factor than the endometrial lesion could be demonstrated in these cases, the significance of postmenopausal proliferation in the endometrium as a possible cause of postmenopausal bleeding is evident. There would seem to be little doubt that this type of bleeding is due to a hormonal mechanism similar to that which brings about the functional bleeding of the reproductive era.

One especially interesting case was included in this group notwithstanding the fact that an ovarian tumor was present. This patient, (case of Dr. R. W. TeLinde), was 62 years old, and had had bleeding for eight months. The preoperative examination disclosed a tumor about the size of a large orange in the ovary. A curetting was done before laparotomy, and this revealed a typical hyperplasia of the endometrium (Fig. 11), so that it seemed highly probable that the ovarian tumor was of granulosa-cell character. However, it proved to be a typical solid fibroma with no suggestion of granulosal or thecal elements.

This case is instructive as emphasizing again the fact that the finding of endometrial hyperplasia in postmenopausal women is not by any means indicative of the granulosal or thecal character of an ovarian tumor, should one be present. Far less does such an endometrial picture warrant the assumption that a tumor of this sort is present even

when it cannot be palpated, as was once urged by some. As our study indicates, postmenopausal hyperplasia not infrequently exists in the absence of tumors of any kind. Furthermore, when hyperplasia is found with ovarian tumors of nonendocrine character, there is far more likelihood that the two lesions are coincidental rather than that the ovarian tumor is responsible for the endometrial change.

Finally, bleeding was a symptom in 8 cases (eliminating 1 case of cervical carcinoma) of the 33 in which a retrogressed hyperplasia of the endometrium was found. In some of these the endometrial condition was found only in old polyps, and it is possible that ulcerative changes in the polyp might have been responsible for the bleeding. Since the hyperplasia pattern in all cases was obviously an inactive one, there is no justification for invoking hormonal factors in the explanation of this type of bleeding.

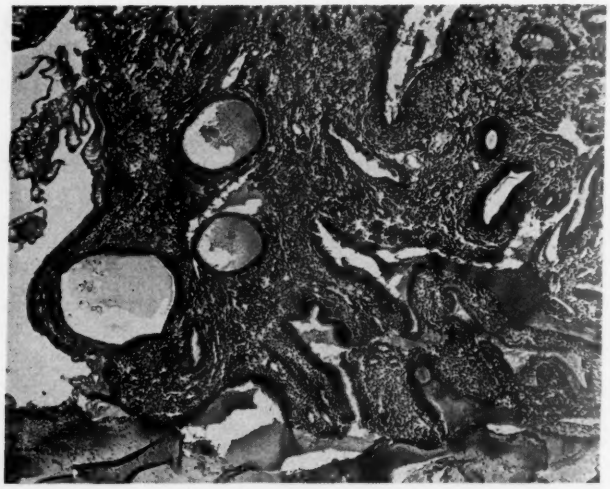

Fig. 11.—Hyperplasia fifteen years after menopause, in patient of 62 years. The presence of an ovarian tumor which proved to be a simple fibroma led to preoperative diagnosis of granulosa cell carcinoma.

The chief interest of this rather considerable group of retrogressive cases would seem to be that they indicate the remarkable persistence of the typical Swiss cheese gland pattern, often for many years after the menopause, and quite possibly throughout the life of the woman. Once this pattern is stamped on the endometrium, as it so often is at the time of the menopause, it appears to remain in a sort of fossilized form thereafter. Menopausal hyperplasia results from an aberration or exaggeration of the anovulatory mechanism, and we believe that the finding of retrogressed hyperplasia long after the menopause is good retrospective evidence that the terminal menstrual mechanism was anovulatory. On the other hand, the finding of an atrophic endometrium would suggest that menstruation and ovulation had come to an end at about the same time; that is, that ovulation had continued to the very end of menstrual life.

Putting our observations together, we would suggest that the varied postmenopausal histology of the endometrium merely reflects the variations in the terminal functional activity of the ovary. If menstruation and ovulation both cease rather abruptly, an atrophic postmenopausal

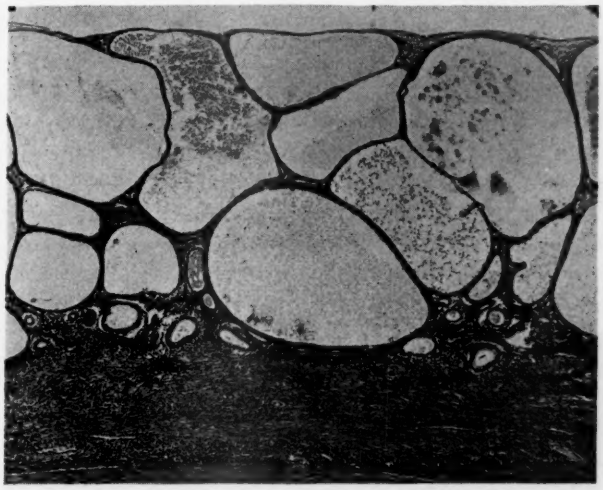

Fig. 12.—Retrogressed hyperplasia three years after menopause, in patient of 57 years. Note extreme cystic enlargement of glands.

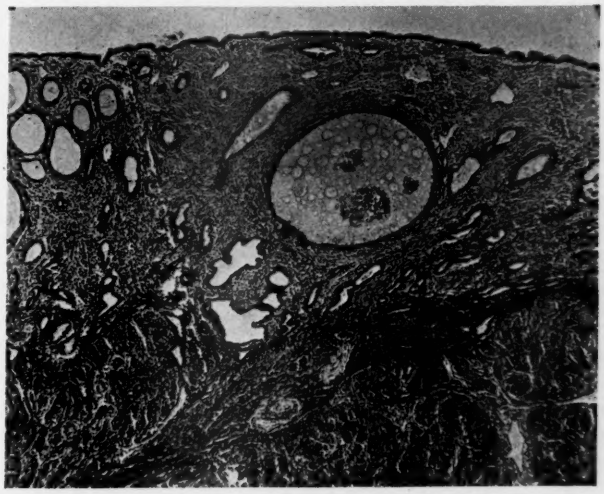

Fig. 13.—Retrogressed hyperplasia, with persisting cystic glands, seven years after menopause, in patient of 49 years.

endometrium may be expected. If, as is so often the case, the terminal cycles are anovulatory, and especially if they are associated with a terminal hyperplasia, as is also common, the hyperplasia pattern may persist for a considerable period of time after the menopause, even in the absence of postmenopausal bleeding. After a variable and indeterminate period, with the complete cessation of estrogen production,

the hyperplasia pattern still persists, although the markedly retrogressive changes in both stroma and epithelium leave no doubt as to the vestigial nature of the process.

One other point deserves mention as regards this inactive, residual hyperplasia pattern which we have encountered so frequently. Most writers stress the frequency of cystic distention of the glands as a feature of senile atrophy of the endometrium, attributing this to occlusion of the ducts by the stromal shrinkage or by inflammation. While this is undoubtedly true in some cases, we do not believe it explains the majority of instances in which marked cystic distention of the glands is found postmenopausally. We are convinced that in the majority of such cases we are dealing with a persistence of the cystic gland enlargement which forms a part of the Swiss cheese hyperplasia pattern (Figs. 12 and 13). We base this view not only on the similarity of the gland pattern, but also on the fact that we have observed all grades of transition between the active and inactive grades of hyperplasia.

SUMMARY

A study was made of 137 endometriums from women ranging from 2 to 40 years after the menopause. Less than one-half of these, 62 cases, showed the atrophic changes usually looked upon as characteristic of the senile endometrium. Fully 42 presented pictures of proliferative activity, moderate in 14, while 28 showed considerable areas of outspoken hyperplasia similar to that seen so often during reproductive life. These findings are no doubt to be linked up with the well-known fact that estrogen may be produced long after the menopause. The source of this postmenopausal estrogen is not definitely known, though it seems reasonably certain that it is not in the ovaries, but rather in some of the other endocrine glands, probably the adrenals.

The endometriums in this series were studied in age groups, showing a striking lack of correlation between the ages of the patients and the histology of the endometrium. The mucosa of some women may show marked atrophy within a few months of the last period, while that of others, 30 or 40 years later, may show striking hyperplasia. The latter, for example, was found in 5 women of 70 or over, the oldest being 87 years.

The clinical importance of these findings lies in the fact that postmenopausal bleeding is a not infrequent symptom in such cases, and it would seem likely that it is due to a hormonal mechanism like that involved in the common functional hemorrhage of the reproductive era.

The remaining 33 cases of this series revealed a histologic picture which we consider to represent a retrogressed hyperplasia. It is characterized by a typical Swiss cheese pattern, but with obvious evidence of retrogression and inactivity, such as fibrosis of the stroma. The significance of this endometrial pattern is that the hyperplasia pattern found in a large proportion of menopausal women persists for many years thereafter, although the causative hormonal factor is no longer operative. Finally, our findings suggest that this residual hyperplasia,

rather than inflammation or stromal cicatrization, is the most frequent explanation of the cystic gland distention so often seen in senile endometriums.

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DISCUSSION

DR. CLARENCE B. INGRAHAM, Denver, Colo.—Assuming that postmenopausal endometrial hyperplasia is the result of estrogenic stimulation, the question of the source of the hormone remains to be answered.

It is not certain that the estrogenic substance found in postmenopausal women and in castrates is identical. It is certain in either case that the supply of hormone is not sufficient to prevent genital atrophy.

Novak and Yui concluded that estrogenic function is probably lacking in senile ovaries. On the other hand, Wallart believes that the menopause signifies cessation of ovulation only and not complete involution.

Herrell states that corpus carcinoma is the result of ovarian estrogenic influence. Carcinoma of the body of the uterus has never been seen, as far as *he* could determine, in a previously castrated individual.

Granulosa and theca cell tumors, and adrenal cortical tumors, are derived from cells having a common embryonic source. The tumor cells can produce sex hormones at any age, before puberty or after the menopause. Estrogenic substance has been extracted from the adrenal cortex. Thus a close relationship must exist between the adrenals and gonads.

Hypothalamic lesions may be associated with precocious puberty. It has been shown by Brooks that transection of the pituitary stalk prevents ovulation in rabbits. Here are indications of a nervous system control of gonadal function, perhaps mediated through the pituitary. It is possible that there is a neuroendocrine difference between the postmenopausal woman and the castrate.

The source of estrogen in the ovary has been shown to be the theca interna cell. Precocious puberty due to an ovarian follicle cyst has been reported by W. F. Mengert. This calls attention to the functional activity of atretic follicles, follicle cysts, and so-called interstitial cells. Maximow and Bloom state that interstitial cells originate from the theca interna of atretic follicles. In the human ovary they soon degenerate and disappear. However, they state also that ovarian stroma cells are not ordinary fibroblasts, being capable of giving rise to other cell types, to decidual cells, to interstitial cells, etc.

Parks, using mice, and Schmidt, using guinea pigs, found growths of cords of epithelioid cells in the ovaries following x-ray, and estrus was not abolished. Schmidt thought the epithelioid cells were the source of estrin. More recently Butterworth found granulosa cell tumors in the ovaries of senile mice following x-ray, apparently developing from normal follicles, following degeneration of the ova.

Such findings as the foregoing led us to inquire into the problem of postmenopausal ovarian activity. Dr. Black and Mr. Polsky of the Pathology Department of the University of Colorado, and I have approached this problem in several ways. *First,* by applying the Foot reticulum stain to a histologic study of senile ovaries, after the plan of Traut and Marchetti in dealing with granulosa cell tumors. They found that with the reticulum stain they could distinguish theca cells, and that most granulosa cell tumors contain them. We found that theca cells can be demonstrated in postmenopausal ovaries, but that they lie singly or in small groups, and that they are not numerous except in granulosa cell tumors.

It is not possible to say from histologic examination whether or not these cells have any estrogenic power. Small to medium-sized follicular cysts are not infrequently found in senile ovaries, sometimes in association with endometrial polyps. The cortical stroma even in completely senile ovaries maintains its peculiar cytologic character.

Second, attempts to apply chemical reactions for estrogens to tissue staining, with the object of identifying estrogenic cells, have so far ended in failure.

Third, slices of human ovary were implanted intraperitoneally in spayed female white rats. With some exceptions, when premenopausal ovaries were used, estrus resulted on the sixth day. Postmenopausal ovarian tissue gave no detectable estrogenic effect. Our series is too small to permit conclusions, but is being extended, and we hope to carry it further.

Drs. Novak and Richardson's paper covers a very important practical field and serves to emphasize the necessity for thoroughgoing study of postmenopausal bleeding.

We believe that it remains to be proved that the senile ovary does not exert some endocrine influence, although it appears entirely possible that estrogenic substances may be formed in the adrenal or elsewhere in the body.

Does endometrial hyperplasia occur in castrates? Our own files do not supply enough cases to answer this question. Also the question raised by Herrell as to whether corpus carcinoma occurs in castrates is pertinent here.

Drs. Novak and Richardson suggest that the varied postmenopausal endometrial picture reflects the variations in the terminal functional activity of the ovary, and we are in accord with this viewpoint, believing that estrogenic activity may persist for a variable time after ovulation ceases.

DR. J. HOFBAUER, CINCINNATI, OHIO (by invitation).—The experimental reproduction of the pattern of endometrial hyperplasia by the repeated intramuscular implantation of bits of anterior pituitary substance (Hofbauer, Surg., Gyn. & Obst., 1931) represented the first attempt to demonstrate that the anterior pituitary registers its intensified effect upon the uterine mucosa through the mediation of the ovary. Subsequently in ovariectomized guinea pigs, using the same experimental technique, proliferative lesions of the basal layer of the uterine mucosa were produced (Hofbauer, J. Obst. & Gynaec. Brit. Emp., 1939).

Such animals showed hyperplastic changes in the adrenal cortex. Hence, it may be assumed that, in the menopause, the proliferative endometrial changes observed may result through the action of estrogenic substances known to be elaborated in part in the adrenal cortex.

DR. HOWARD C. TAYLOR, JR., NEW YORK, N. Y.—The assumption seems to have been made that late epithelial proliferation of the endometrium must be due to a persistent or recurrent estrogenic function. Such proliferation may, however, be caused by other types of stimuli, perhaps localized in the uterus such for instance as that which causes polyps. It is indeed possible that some of these signs of proliferation reported by Dr. Novak are localized tissue changes similar to that seen in polyps but which have not attained the polypoid form.

I would like to ask Dr. Novak whether the proliferative changes reported by him were widespread throughout the endometrium, or were more localized. In the latter case the proliferation might represent the beginnings of polyps or similar sessile growths and not a general endometrial response such as one would expect from a hormone stimulus.

DR. HERBERT F. TRAUT, NEW YORK, N. Y.—For some years we have been making routine vaginal smears in all our patients and we have of course dealt with a large number of women in the postmenopausal period. We have learned that there is a tremendous difference in the response of the cervical and vaginal cells which find their way into the smears. These variations are not entirely dependent upon the available estrogen. There seem to be factors other than the estrogen which have much to do with the function of the female genital tract. What those factors are we do not know, but we have many reasons to believe that the menopause is characterized by different hormonal stimuli taking over as the estrogens pass out of the picture more or less completely.

DR. NOVAK (closing).—Most of the discussion has centered around that aspect of the paper which we least emphasized and concerning which we know little, namely the nature and the source of the estrogenic stimulus responsible for the postmenopausal proliferative changes in the endometrium. While the senile ovary may be the source of the causative estrogen, we think this very unlikely, for reasons we have discussed in our paper. An origin from one of the other endocrine glands, perhaps the adrenal cortex, seems more likely.

The hyperplasia of postmenopausal life is often localized. During reproductive life, however, it likewise may occur in limited areas, as seen so characteristically in polyps with the typical Swiss cheese pattern. Wherever hyperplasia occurs, however, there is ample evidence, experimental and otherwise, that it is due to estrogenic stimulation. In fact, no other cause has, so far as I know, been suggested by any one, and I therefore do not know what type of "local factors" Dr. Taylor has in mind as causing endometrial hyperplasia. If we were discussing bleeding, such as that seen with some polyps, the question would be a very different one.

Dr. Hofbauer's reference to the underlying role of the pituitary is also in accord with the accepted view of the dominance of this gland over the endocrine function of the ovary. He refers to his results, as yet unconfirmed by others, on a direct proliferative effect of the pituitary on the basal layer of the endometrium. On the other hand, numerous investigators have been able to produce hyperplasia in castrated women or animals by means of adequate estrogenic stimulation, so that there would seem to be no question that estrogen is the immediate factor concerned in the production of this endometrial picture.

A COMPARATIVE ANALYSIS OF TOTAL ABDOMINAL, SUPRAVAGINAL, AND VAGINAL HYSTERECTOMIES*

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THIS study comprises a survey of hysterectomies done on the Tulane University Gynecological Service of Charity Hospital, during the years 1939 and 1940. The series represents a total of 828 consecutive hysterectomies. We purposely divided and kept segregated the data obtained from each of the two years' work studied, in an effort to prove the definite, growing conviction that total hysterectomy, either by the transabdominal or the vaginal route, warrants its position of priority. A separate analysis of the white and colored services was undertaken in order to attempt an evaluation of the relative safety of the three types of hysterectomy in the colored woman, in whom the pathology which necessitates surgery is always of a more gross and extensive nature.

The evidence accumulated through the study of this and other large series of hysterectomies, leaves little basis for controversy as to the relative superiority of total over supravaginal hysterectomy in most cases. Complete removal of the uterus, where such surgery is indicated, has become increasingly popular and is the method of choice with most gynecologists for several reasons: (1) The mortality and morbidity rates for total hysterectomy are as low as, or lower than, those encountered in an equal number of supravaginal amputations. (2) In from 12 to 15 per cent of the cases in which the cervix is not removed, intractable leucorrhea, pelvic pain, and backache cause the patient to return subsequently for cauterization, conization, or removal of the cervical stump. (3) The cervix may harbor a focus of infection from which such metastatic lesions as arthritis, myositis, and iritis may result. (4) The frequency of the development of carcinoma on the cervix following subtotal hysterectomy is difficult to estimate; the literature records the incidence variously as from 1 to 7 per cent. Even if the smaller figure is correct, such a cancer risk should obviously influence the gynecologist to select the complete type of operation in all cases where it is feasible.

Prolapse of the vaginal vault, shortening of the vaginal canal, and dyspareunia are objections which have been offered to total hysterectomy, but which we feel have little valid justification. No apprehension need be felt that a prolapse of the vagina may occur following complete hysterectomy if the severed cardinal, uterosacral, round, and broad ligaments are sutured accurately to the lateral margins of the vaginal cuff, and if a reconstruction of the perineal and bladder supports is also done.

*Read at the Sixty-Sixth Annual Meeting of the American Gynecological Society, Colorado Springs, Colo., May 26 to 28, 1941.

There need be little or no sacrifice of the length of the vaginal canal if care is exercised in severing the vaginal cuff close to its attachment to the cervix. Indeed, the depth of the vagina may be actually increased by dissecting the vaginal mucous membrane loose from the cervix, and, by traction, peeling this layer away from the portio almost to the opening of the external os, before the vaginal canal is invaded.

Dyspareunia is an infrequent complaint following total hysterectomy, in our experience. When it has occurred, it has resulted from limitation of the elasticity of the vaginal vault occasioned by overshortened, and consequently rigid, ligaments being fixed to the vaginal cuff; from an ovary being dragged too deeply into the pelvis and immobilized by an improperly placed suture; from the formation of adhesions between a segment of the small bowel and the operative field; from a failure to peritonize all raw surfaces; or lastly, from an incorrect realignment of perineal supports when vaginal plastics are done coincidentally.

Total abdominal hysterectomy and vaginal hysterectomy are the operations of choice with the gynecologist, but there is no gainsaying the fact that they are surgical procedures of some magnitude and should not be undertaken by a novice. If the experience of the operator is limited and if his knowledge of pelvic anatomy is not absolute, it is far safer for him to elect the supravaginal type of operation, because it is technically more simple, and serious postoperative sequelae are less likely to occur.

Cauterization of the cervix combined with subtotal hysterectomy can never, and should never, replace total abdominal hysterectomy. This statement is based upon the personal observation of several instances in which the combined procedure has been most unsatisfactory. The frequency with which the cervical stump has to be removed, due to a continuation of the patient's complaint, long after supravaginal hysterectomy and combined cauterization and plastic on the cervix have been performed, certainly offers evidence that neither cauterization, repair, nor reconstruction of the cervix can be associated with subtotal hysterectomy as a satisfactory substitute for the total removal of the uterus. The gynecologist who would claim superiority for cauterization of the cervix in association with subtotal hysterectomy admits the fallacy of his logic in the claims which he advances, for certainly, if the cervix is so diseased as to require cauterization, it is far better removed.

The comparative percentages of incidence of the three types of hysterectomy in the total series of 828 cases is summarized in Table I.

TABLE I. INCIDENCE OF VARIOUS TYPES OF HYSTERECTOMY IN 828 CASES

TYPE OF HYSTERECTOMY	NUMBER OF CASES	PERCENTAGE OF INCIDENCE
Total abdominal	374	45.2
Supravaginal	255	30.9
Vaginal	199	23.9

It will be observed that in these 828 cases in which it was thought hysterectomy was indicated, complete removal of the uterus was done abdominally or vaginally in 573 cases, or in 69.1 per cent.

While it is the conviction of the staff that total hysterectomy is the preferable procedure in performing transabdominal hysterectomy, it was found necessary to compromise and resort to supravaginal amputation in 30 per cent of the total number of cases. In explanation of this, we might point out that supravaginal hysterectomy was performed in 188 of the 372 colored cases, as compared with 67 of the 456 white cases. Thus, the ratio of incidence of subtotal hysterectomy to total hysterectomy in the colored and white cases was 3 to 1, respectively. This high ratio of incidence for subtotal hysterectomy in colored women was due to several factors. A large percentage of these colored patients have extensive adhesions and residual exudates resulting from repeated pelvic infections. The fibroids present are not only of multiple type, but are usually of gross dimensions and practically always show extensive degenerative changes. Categorically speaking, the colored woman rarely seeks an explanation for even a protracted menorrhagia, but rather waits for the intervention of pain before consulting a doctor, when the fibroids have become very large, or when adhesions and exudates have become widespread from repeated attacks of salpingitis. Secondary anemias, arteriosclerosis, and myocardial disease, and the high percentage of syphilis, are all factors which render the colored woman less surgically fit for the more radical type of operation. Confronted with extensive adhesions, large fibroids, or similar complicating factors, senior residents, who have been permitted operating privileges without supervision, frequently elect the subtotal in preference to the total operation. A large number of the subtotal operations were performed by them under these circumstances.

For the same reasons, vaginal hysterectomy was elected infrequently in the colored women. Vaginal hysterectomy, a popular procedure on our service, has lost some favor in the last two years because of the frequency of postoperative urinary complications. It is also the conviction of the staff that this procedure, although it can be accomplished in almost any woman, is not satisfactorily performed except where there is beginning prolapse of the uterus and reasonable mobility of this structure. Its performance, as advocated by a few men, in the presence of a fixed uterus, salpingitis, or large fibroids, increases the operating time and the operative trauma, and makes the removal of the uterus, which might have been simple and easy if undertaken abdominally, a time-consuming, bloody, and laborious task, and the end-results under these circumstances are by no means universally desirable.

A study of the comparative frequency of the three types of operation in the colored and the white woman brings out some interesting information (Table II).

These figures evidence the growing popularity of total over subtotal hysterectomy in our service, as there was an increase from 25 per cent total hysterectomies in 1939, to 50 per cent in 1940 in the colored cases, and from 39.6 in 1939 to 51.1 per cent in 1940 among the white cases. This increase in the number of total abdominal operations was not due to a neglect of the vaginal approach, as the percentage of vaginal hysterectomies remained approximately the same for the two

TABLE II. INCIDENCE OF VARIOUS TYPES OF HYSTERECTOMY IN 456 WHITE AND 372 COLORED WOMEN

TYPE OF HYSTERECTOMY	1939		1940		TOTAL
	CASES	%	CASES	%	
White					
Total abdominal	73	39.6	139	51.1	212
Supravaginal	35	19.0	32	12.1	67
Vaginal	76	41.4	101	36.8	177
	184		272		456
Colored					
Total abdominal	34	25.0	128	50.0	162
Supravaginal	94	61.7	94	39.8	188
Vaginal	8	13.3	14	10.2	22
	136		236		372

years, and the actual number of vaginal hysterectomies performed increased considerably in 1940 as compared to 1939. It is interesting to note that in the entire series of colored patients, vaginal hysterectomy was the type of operation chosen in only 22 cases. The reason for this low incidence has already been commented upon.

The large increase in the total number of hysterectomies performed in 1940, as compared with the total number of hysterectomies performed in 1939, was not due to any widening of the indications for hysterectomy on our part, but was due entirely to the fact that the number of beds in our service had been doubled upon occupation of the new Charity Hospital building.

There were 14 deaths in the series, accounting for a total mortality rate of 1.6 per cent. Dividing these deaths among the three types of hysterectomy, reveals data as to mortality as shown in Table III.

TABLE III. MORTALITY OF VARIOUS TYPES OF HYSTERECTOMY IN 828 CASES

TYPE OF HYSTERECTOMY	NO. OF CASES	NO. OF DEATHS	MORTALITY RATE
Total abdominal	374	5	1.33%
Supravaginal	255	7	2.75%
Vaginal	199	2	1.0 %

I might add parenthetically that the mortality rate for the 1940 series of 267 abdominal operations was 0.75 per cent. This low death rate is due, I believe, to better operating room facilities, better preoperative care, particularly more careful preparation of the vaginal tract, and to improved operative technique.

While the death rate in supravaginal operations has been higher than in total abdominal hysterectomies, it must be taken into consideration that a fair percentage of the subtotal hysterectomies were performed on patients who had extensive pelvic adhesions, and upon patients who, for other reasons, were considered bad risks. The factor of the individual skill of the separate physicians also plays some part, and it would have been interesting to compare the mortality of residents' cases against the mortality of staff cases, etc., but this was not determined.

The factor of anesthesia should also be considered in its effect upon mortality, and it may be mentioned that, with the exception of some few cases of spinal anesthesia, all of these patients were anesthetized by graduate nurses who are students in anesthesia. Three of the deaths in the entire series were considered as anesthetic in origin. In addition, another three deaths may be regarded as due to factors not associated with the surgical procedure, since one of these patients died of a proved coronary thrombosis (autopsy) another (a cardiac patient) died forty days postoperatively from acute dilatation of the heart, and the last died six weeks postoperatively from bronchopneumonia and pyelonephritis. No attempt has been made to correct the mortality figures given.

An attempt was made to determine the morbidity rate of these types of hysterectomy, based on the number of hospital stay-days and temperature runs of 100.4° F. for three successive days, not counting the first postoperative day. The number of normal postoperative stay-days was set arbitrarily at fourteen days for total abdominal and vaginal hysterectomies, and at twelve days for supravaginal.

Total Abdominal Hysterectomy—374 Cases:

287 cases 76.9% had estimated normal hospital stay-days.
87 cases 23.5% remained longer than estimated normal stay period.

Supravaginal Hysterectomy—255 Cases:

164 cases 64% had estimated normal hospital stay-days.
91 cases 36% remained longer than estimated normal stay period.

Vaginal Hysterectomy—199 Cases:

143 cases 71.8% had estimated normal hospital stay-days.
56 cases 28.2% remained longer than estimated normal stay period.

Temperature records for the three types of operation were:

Total Abdominal Hysterectomy—374 Cases:

296 cases 79.1% had no morbid temperature runs.
78 cases 20.9% had morbid temperature runs.

Supravaginal Hysterectomy—255 Cases:

211 cases 82.7% had no morbid temperature runs.
44 cases 17.3% had morbid temperature runs.

Vaginal Hysterectomy—199 Cases:

143 cases 71.7% had no morbid temperature runs.
56 cases 28.3% had morbid temperature runs.

Analyzing the specific causes of morbidity in the three types of hysterectomy showed that urinary infection was the prime cause of increased stay-days and temperature elevation, and was present in the following percentages of cases:

Total abdominal hysterectomy	41.3%
Supravaginal hysterectomy	28.5%
Vaginal hysterectomy	69.3%

Wound infection came second with:

Total abdominal hysterectomy	22.6%
Supravaginal hysterectomy	18.6%
Vaginal hysterectomy	13.4%

Other causes of morbidity, singly or combined with the above factors, were postoperative vaginal bleeding, thrombophlebitis, postoperative irradiation following operations for carcinoma of the fundus and malignancy of the ovaries, localized peritonitis, diabetes, partial obstruction, hypertension with myocardial disease which required the patients to remain in the service for further care from the medical staff after operation.

How to reduce the high rate of postoperative urinary infections remains a controversial issue. If, when, and how often to catheterize? Should bladder irrigations be resorted to, or should chemotherapy be relied upon entirely? Should retention catheters be inserted, and how long should they remain? All these types of prophylactic and active treatment of urinary infections have their advocates, with about the same ultimate results. It is worthy of note that in the total abdominal and vaginal types of hysterectomy, where the bladder is apt to be traumatized most, the incidence of urinary infection is highest.

It is our impression that this high incidence of urinary infection is due, in some degree, to an overworked nursing staff in a public institution, where the ratio of patients to ward nurses is exceptionally high, and prompt catheterization of the individual patient is almost impossible. Postoperative retention is consequently common. The use of indwelling catheters has decreased the urinary retention, in the cases employed, but has not appreciably altered the incidence of infection. It would seem advisable, in the future, to consider the possibility of urinary infection before operation, rather than immediately afterward. In this light, the bladder of every woman who presents a cystocele is either already infected or predisposed to infection. A series of bladder irrigations preoperatively, rather than postoperatively, would seem advisable, and, in addition, the administration of urotropin and an acidifying agent in appropriate doses for several days preoperatively up to the date of operation would increase the incidence of spontaneous urination due to the increased vesical tone which would result. In several private cases, this procedure has been most satisfactory.

We were surprised to find such a large number of wound infections, but on careful study of the charts it was found that all wounds were classified as infected in which there was any evidence of failure to heal primarily, or in which there was only a slight amount of pus about a retention or skin approximation stitch.

An interesting and gratifying finding was that in the total abdominal and vaginal hysterectomies, twelve cases of very early carcinoma of the cervix were reported as being found in the microscopic survey of the tissues submitted to the Pathological Department. On the other hand, we are not aware of the subsequent development of this lesion on the cervix of any of the cases for whom a supracervical amputation was done.

The number of incidental vaginal plastic operations done in this series were:

Total abdominal hysterectomy	91 cases	10.7%
Supravaginal hysterectomy	56 cases	6.7%
Vaginal hysterectomy	199 cases	100.0%

We were unable to find any reason to feel that an additional plastic procedure added any particular risk to the surgical procedure, or increased the postoperative morbidity beyond some additional discomfort and the necessity for catheterization in a larger number of cases.

Surgery other than hysterectomy was necessary in 30 per cent of colored and 18 per cent of white cases in the total abdominal group, and in 40 per cent of the colored and 12 per cent of the white cases in the subtotal hysterectomy group. Additional operative procedures were salpingectomy, oophorectomy, releasing of adhesions, cauterization of isolated areas of endometriosis, repair of incisional hernias, temporary colostomy, repair of accidental injuries to the bladder. The latter occurred five times in the series. In four cases, the rent in the bladder was closed immediately with complete success. In the fifth case, the left ureter was ligated in doing a complete hysterectomy and a ureterovaginal fistula developed postoperatively. The damaged ureter was recently successfully implanted in the bladder.

Incidental appendectomy was performed in 45 per cent of the total abdominal group, and in 43 per cent of the subtotal group. How many cases had had previous appendectomy was unfortunately overlooked in the preparation of these data. It is our custom to remove the appendix following hysterectomy in all cases except those in which the hysterectomy has been tedious and time consuming; or in which the removal of extensive adnexal pathology has prevented proper peritonealization of all raw surfaces; or where, because of some general condition, the patient was thought to be none too good a surgical risk.

From the foregoing data, we feel justified in submitting the following conclusions:

1. Hysterectomy, regardless of the type, is a comparatively safe surgical procedure when done by the trained specialist.

2. Total hysterectomy is the preferable type of transabdominal approach, because with the removal of the cervix such postoperative sequelae as leucorrhea and chronic foci of infection are removed, and the subsequent hazard of carcinoma of the cervix is eliminated. The mortality in the group of total hysterectomies studied was lower, and the morbidity rate was only slightly higher than those of the subtotal group.

3. Subtotal hysterectomy should be the procedure of election in cases in which the pathology is extensive and necessitates a tedious and time-consuming operative procedure, or if the experience of the surgeon is limited.

4. Vaginal hysterectomy deserves its position of popularity because of its relative safety, the fact that there is less postoperative shock and distention, and because of the excellent end results obtained. We feel, however, that such results are obtained only when the conditions previously mentioned are present, which render the technique of vaginal hysterectomy comparatively simple.

3439 Prytania Street

TOTAL HYSTERECTOMY, ABDOMINAL AND VAGINAL*

W. C. Danforth, M.D., Evanston, Ill.
(From the Evanston Hospital)

FOR many years the most frequently employed method of removing the myomatous uterus or of excising the uterus for a number of other common causes has been subtotal hysterectomy. The amputation of the uterus is performed at the level of the internal os or below it unless it is desired to leave enough endometrium to cause some loss of blood at the menstrual periods, when the excision is done at a varying level above the internal os. The history of the operation of hysterectomy occupies just less than one hundred years, for it was in 1844 that Attlee removed the uterus for myoma for the first time. The mortality of the operation has steadily decreased as technique has improved and experience has grown until, in good clinics today, it is done with a high degree of safety.

Of late years it has become the practice in some clinics to remove the entire uterus, including the cervix in many and perhaps the majority of cases. Opinions are still divided upon the question of the wisdom of using the more extended operation as a routine procedure and many clinics still make use of supravaginal excision as the usual operation, reserving the total operation for cases in which malignancy is suspected or is known to exist, or for patients whose cervices are notably unhealthy. The argument in favor of the more extended operation has revolved largely about the question of carcinoma in the retained cervical stump.

For many years my associates and I were quite definitely of the "subtotal school," removing the cervix when operating abdominally only when carcinoma of the corpus was being dealt with or when the cervix was markedly unhealthy. Some years ago we began to make much more use of the vaginal hysterectomy than we had done. As we accumulated a series of vaginal hysterectomies of some size we began to be impressed with the fact that the women who had the entire uterus removed, as it is in the vaginal operation, came back to us far less frequently for treatment of discharges and bleeding from the retained stump than was the case in our patients upon whom the subtotal operation had been done. Not only because of the risk of cancer in the retained stump but also to free our patients from the results of retention of the frequently unhealthy cervix, we began to make much more frequent use of the total excision of the uterus in those patients who are operated upon abdominally.

The debate as to the value of the total operation is not a new one.

*Read at the Sixty-Sixth Annual Meeting of the American Gynecological Society, Colorado Springs, Colo., May 26 to 28, 1941.

In 1921 John O. Polak collected 900 cases of total hysterectomy from the clinics of Schottlaender, Herbert Spencer and Noble, among which were found 2 per cent of carcinomas. Since that time the question has been argued at various times. Von Graff in 1934 collected 1,169 cases of carcinoma of the stump of the uterus after subtotal hysterectomy. If this number can be found in the literature or obtained by inquiry directed to known workers in the field of gynecology, the number of cancers after subtotal hysterectomy is sufficiently great to arouse our active interest. It is generally assumed that the incidence of carcinoma in the retained stump is about 2 per cent; Richardson believes the incidence to be 3 per cent. Masson reports that, of 1,489 cases of carcinoma of the cervix seen at the Mayo Clinic, 65, or 4.4 per cent, were stump cancers. Henriksen, who studied 940 cases of cancer at the Johns Hopkins Hospital, found 2.3 per cent of them to be cancers of the retained stump. Behney reported 910 cases of cervical cancer at the University Hospital in Philadelphia and found 43 cases of cancer of the retained stump, or 4.7 per cent. He also reported 1,117 cases of cervical cancer at the Philadelphia General Hospital, of which 24, or 2.15 per cent, were cancers of the stump. Ward saw 61 stump cancers, or 6.9 per cent, of 879 cancers of the cervix.

That carcinoma of the cervical stump is a real danger and that it occurs with a disturbing frequency must be admitted. The surgeon who has not seen such a case in his own practice may feel that this danger is an overrated one but he forgets that many patients, who have trouble after any surgical procedure, are likely to seek advice from some one other than the original operator, who, they may conclude, has not met the situation completely.

TABLE I. INCIDENCE OF STUMP CANCER

	NO. CASES CA. CERVIX	NO. STUMP CA.	PER CENT
Masson	1,489	65	4.4
Henriksen	940		2.3
Behney—Univ. Hosp.	910	43	4.7
Behney—Phila. Gen.	1,117	24	2.15
Ward	879	61	6.9
Total	5,335	193	4.01

In addition to the risk of cancer, the retained stump may be troublesome in other ways. Endocervicitis or cervicitis is prone to develop and many of these women complain of leucorrhea later. The circulation of the cervix is disturbed and it responds poorly to treatment. Polyps sometimes develop and require removal, and troublesome bleeding due to inflammatory damage to the cervix may appear. I have had to remove a number of cervical stumps, some of which were in patients operated upon by me and some of which had been done elsewhere, either because of bleeding or to eliminate a possible source of infection.

The comparative risk of the two operations is often urged in favor of the subtotal operation. It is freely admitted that in the hands of men who do only an occasional hysterectomy the subtotal procedure is to be preferred. Our own experience and the reports in the literature,

however, indicate clearly that in the hands of expert pelvic surgeons the two operations are of equal safety. Masson reports a series of 3,149 hysterectomies of which 1,776 were total, 766 subtotal, and 607 vaginal. The mortality of the total operations was 1.2 per cent, of the subtotal 0.9 per cent, and of the vaginal hysterectomy 1.5 per cent. If the total operation is to be advocated for use in the hands of experienced gynecologic surgeons it must be shown that in their hands it carries a risk which is less than that of the later development of cancer in the stump. The figures just given indicate that the difference is far less than the 2 or 3 per cent which is the incidence of the occurrence of carcinoma in the retained stump. I wish to make it clear that in advocating the removal of the entire uterus I do not mean to imply that all cases should be done by the abdominal route. Vaginal hysterectomy accomplishes the object of removing the cervix, and it was the comparative freedom of our patients who had been operated upon by the vaginal route from annoying discharges and bleeding as well as from the risk of later cancer which directed our attention to the total abdominal operation in cases which were unsuited to attack by the vaginal path. Since making use of the total abdominal operation frequently, we have operated upon 150 women by this method with one death, a mortality of 0.66 per cent. The mortality in a series of 744 subtotal hysterectomies was 0.8 per cent.

TABLE II

	NO.	MORTALITY	MORBIDITY
Subtotal	744	0.8 %	28.0%
Total abdominal	150	0.66%	33.0%
Vaginal	425	0	42.5%

We have removed the uterus vaginally, since adopting this procedure as one of our usual methods, 425 times. The discrepancy in the number of the two operations arises from the fact that the total abdominal operation has been used over a far shorter time than the vaginal operation. In a large series studied by Smith 35 per cent of the hysterectomies were vaginal. Both the vaginal operation and the total abdominal one accomplish the elimination of the cervix and that one should be used which best adapts itself to the case in hand.

In a series of 1,200 hysterectomies analyzed in our service by P. H. Smith the entire mortality was 0.5 per cent and all the deaths were in the subtotal group. This may be accounted for by the fact that during much of the time covered by this study we did more subtotals than any other sort of operation and by the further fact that many of the most difficult cases were done by this method. That we have so far not had a death after vaginal hysterectomy we attribute in some measure to good fortune although all possible precautions are observed and the men in the group are all well trained. It should be said that the majority of these patients were private and that the incidence of severe and extensive inflammatory residues is less than in a large charity service. There is no provision for colored patients, those in our out-patient clinic being cared for elsewhere. This has its effect on the mortality of

both the abdominal and the vaginal operations. The morbidity of the total hysterectomies was 33 per cent, that of 744 subtotal operations studied by Smith was 28 per cent, and that of the vaginal series 42.5 per cent. In spite of the fact that there is a little more fever in the total and the vaginal groups it is notable that convalescence is no less smooth than that of the subtotal operation. By whatever route the uterus is extirpated one passes through an area which is not aseptic. The subtotal operation requires the cutting across of the cervix, which, if it be at the level of the internal os or lower, is a bacteria-containing field. A painstaking preparation of the vaginal field is an essential part of the preparation for either the total abdominal or the vaginal operation.

That the elimination of the cervix is a desirable thing is indicated by a survey of the pathologic reports of the cervices removed in 124 cases. Of these the pathologist reported that 61 showed major abnormalities, as marked eversion, endocervicitis or polyps; 32 were unhealthy to a lesser degree but did have endocervicitis and erosion or eversion; 5 had an atresia in some part of the cervical canal, in one a small myoma was found and 25 were relatively normal. At least half of the cervices of women at the age at which some condition exists which causes the surgeon to consider hysterectomy are unhealthy.

Coning out of the cervix has been urged as a means of protecting the patient against the dangers and disadvantages of the retained cervical stump. About 80 per cent of the stump cancers are epidermoid in type. The process of coning out removes only the epithelium of the canal leaving that which is most likely to be dangerous later on. Bleeding is more likely after an operation in which this measure is used. After trying it in a series of cases some years ago I discarded it as an inefficient procedure. The performance of a cervical plastic followed by a subtotal hysterectomy requires a longer period of anesthesia than a total operation and leaves behind a mass of cervical tissue which may still be troublesome.

It has been urged that the removal of the cervix deprives the vagina of support. This statement is based on an erroneous conception of the mechanics of support of the pelvic structures. If the vagina is in real need of support, an operation should be done, preferably from below, which has for one of its objects the correction of this condition. If the pelvic supports are essentially normal, the vagina may be cared for just as is the cervical stump by the use of the supporting structures of the upper pelvic floor. Dyspareunia will not occur if this is not too tightly done and if the ovaries are not fastened to the vaginal vault.

I have operated upon several cases in which subtotal hysterectomy had previously been done and in which the cervical stump came down. In these cases the corpus had been removed for menorrhagia or for a small myoma while nothing was done for co-existent descensus. Whether the cervix remains or does not remain, a lack of support must be cared for if it is present.

The shortening of the vagina, which has been urged against the total and the vaginal operation, does not seem to me to be a valid objection. In a considerable series of total abdominal and vaginal operations we have had no complaints of this. It is true that in some cases operated

upon vaginally for prolapse there is some shortening but a vaginal adequate for all demands upon it will remain after total excision of the uterus both abdominally or vaginally in cases of other types.

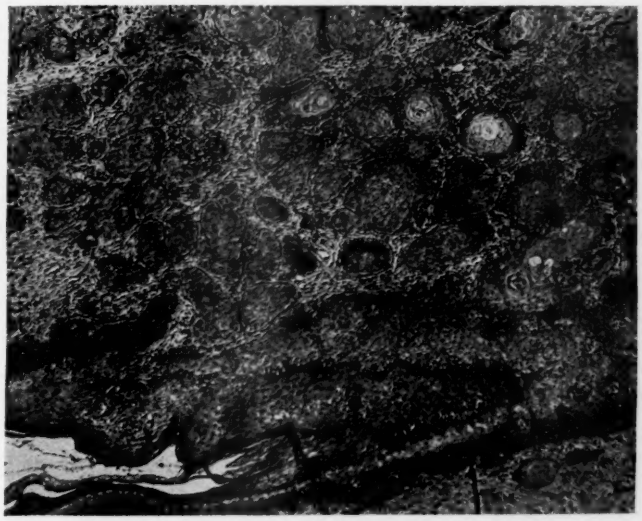

Fig. 1.—Unsuspected carcinoma of cervix found after complete hysterectomy.

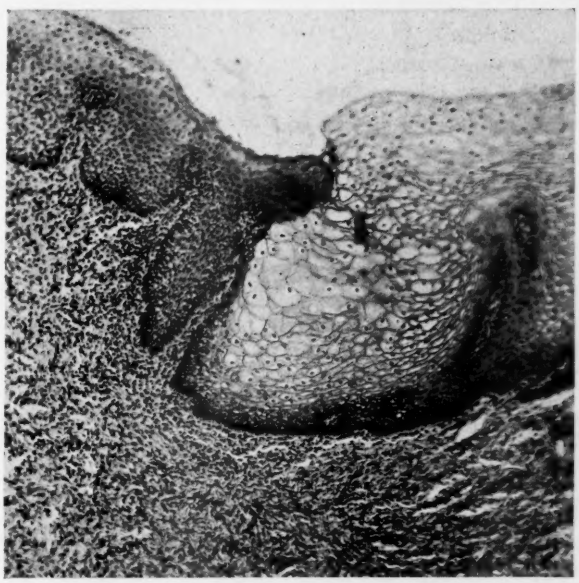

Fig. 2.—Biopsy specimen showing "Schiller's line."

The dryness of the vagina which has been charged against total removal seems also to be infrequent as we have had no patients who have been troubled in this way. If the ovaries are left in a normal condition, with an adequate blood supply, the vaginal mucosa will remain normal.

It is quite true that in the hands of the occasional operator, or in those of the surgeon who does but few hysterectomies, the subtotal operation is to be preferred. Masson estimates the risk of the subtotal operation in the average hospital as about 4 per cent and that of the total one as 6 per cent. The mortality of subtotal hysterectomy in active and well-staffed clinics is much less than this. Fullerton and Faulkner found that there was a definite difference in the mortality in total cases done by the attending staff and those done by the residents. This would indicate that in the hands of the untrained or the partly trained surgeon the danger of the total operation is greater than when it is done by the experienced pelvic surgeon.

Our own experience and the reports which are available in the literature indicate that the experienced pelvic surgeon can do either the total or the subtotal operation with essentially the same risk, and we have found that the vaginal approach provides a safe and excellent means of disposing of the uterus in many cases. The trained gynecologist can easily develop his technique so that he will do the more extended operation with almost equal ease and with but little more expenditure of time. Lengthy operations are far more productive of shock than are those which are more expeditiously carried out. The man who requires over two hours for the performance of a subtotal operation had better not venture into the total field and the vaginal operation, too, may be better left alone. The gynecologist should be able to do any of these and to complete his work, except in an occasional case of great difficulty, in less than an hour. The risk of wounding the ureters in total abdominal operations is not great if one keeps close to the uterus. It is not necessary to expose them in the great majority of cases. Sufficient light, proper exposure, and nontraumatic management of the bladder and the structures about the cervix will enable the operator with an adequate knowledge of pelvic anatomy to work safely and expeditiously.

One point only of technique will be mentioned. When we did total operations only occasionally, as for carcinoma of the corpus, we were accustomed to drain vaginally. This has long since been given up and at present no drains are used in either the abdominal or the vaginal removals of the entire uterus. The drain is unnecessary and it increases the danger of adhesions. A local peritonitis surrounds the point of which it leaves the abdominal cavity and this may cause the adhesion of a loop of bowel. While the operation of removal of the uterus, by any method, causes an area in which bacteria are found to be opened, the pelvic peritoneum cares for such bacteria as may gain entrance to the peritoneal cavity very efficiently so long as they are confined to one area and not spread about. The only cases which require drainage after the removal of the entire uterus are those of vaginal operation for prolapse in which much dissection is done. In these a small strip of rubber tissue lessens the likelihood of hematoma.

It is generally assumed that a carcinoma which appears in the cervical stump within one year after subtotal hysterectomy was already present at the time of the operation. It is probable that this time limit is too short. Within the past year, in a patient operated upon by one of my

associates for small fibroids and menorrhagia, a very small clinically unrecognized carcinoma was found. A study of cervices of cases dealt with by the removal of the entire uterus disclosed many which were definitely abnormal. Whatever the relationship of these changes to cancer, it may at least be said that an unhealthy structure has been done away with. Some of these show an epithelial activity, which, while not cancerous, at least indicates an activity which is not normal.

It is notable that we have had no cases of embolism and phlebitis after vaginal hysterectomy and I believe that in two other well-known gynecologic services, in each of which a large number of vaginal hysterectomies have been done, no embolism or phlebitis has appeared. Should continued experience in a number of clinics bear out this observation it may well be regarded as an added reason for the employment of this procedure.

In about 3 per cent of myomatous uteri coincident adenocarcinoma may be found. As more hysterectomies are done for myomas than for any other single reason the removal of the entire uterus is wise unless the carrying out of the total operation subjects the woman to a risk greater than the incidence of cancer. This, in experienced hands, will not be so.

The complete removal of the uterus, abdominally or vaginally, for many benign conditions as well as for carcinoma of the corpus, should be done more frequently by experienced pelvic surgeons, inasmuch as, in their hands, the patient runs no added risk. In institutions in which but little gynecologic surgery is done, the subtotal operation will be safer.

CONCLUSIONS

1. To avoid the danger of cancer in the retained stump and to free the patient from the annoyance which may be caused by the unhealthy stump, a wider use of the total removal of the uterus is recommended.
2. Total hysterectomy may be done either abdominally or vaginally, as the conditions of the individual case may suggest.
3. The gynecologic specialist should be able to remove the uterus either abdominally or vaginally with sufficient ease that his choice of operation is not influenced by his lack of experience with one or the other nor should he choose the incomplete operation instead of either because he feels that he can do it more easily.
4. Technique of either of these operations may be developed by the experienced operator.
5. The objections which have been urged against the complete removal of the uterus disappear if a proper technique is used.
6. Total removal in experienced hands, either abdominally or vaginally, does not subject the patient to increased risk.
7. The operator of small experience in pelvic surgery should make use of the subtotal operation.

636 CHURCH STREET

DISCUSSION ON PAPERS BY DR. MILLER AND DR. DANFORTH

DR. RICHARD W. TELINDE, BALTIMORE, MD.—I believe that total hysterectomy should be done more frequently than it has been done in the past. I believe that if done by the proper technique it can be done without appreciable shortening

of the vagina and that the vagina can be just as well suspended as the cervical stump. I also believe that by cutting close to the cervix, especially by using the Richardson technique, the danger of injury to the ureters and bladder is minimal. But I wish to go on record as not favoring the *routine* employment of total hysterectomy. I believe with Dr. Miller that each case should be judged individually, the chief points to be considered being the condition of the cervix, the general condition of the patient, the presence or absence of obesity, and the intrapelvic pathology.

During the past year we have performed approximately 400 abdominal hysterectomies on our service, 74 of which were totals. Over half of these were performed on colored women who are frequently obese and have difficult myomas complicated by salpingitis. We lost one patient by pulmonary embolism, a mortality of a quarter of 1 per cent. There were no deaths among the panhysterectomies. These statistics indicate to me that proper judgment was exercised in choosing the cases for total hysterectomy, for if the operators had insisted upon removal of the cervix in some of the difficult, complicated myomas, I am sure our mortality could not have been held down to such a low figure.

In private practice the conditions are much more favorable to total hysterectomy and I do that operation in approximately half of my cases. However, I still prefer to save the nulliparous and slightly lacerated parous cervices which look healthy and are not the source of leucorrhea, for I believe in the surgical principle that the least amount of surgery to cure the patient is the best.

I think that Dr. Danforth's figure of an incidence of 2 per cent of malignancy in the retained cervical stump is high. This figure *must* be an estimate, for the only way an accurate figure could be obtained would be to follow a large series of women to death upon whom subtotal hysterectomies had been done. I do not believe this has ever been carried out. This figure must of course not be confused with the incidence of stump cancer in cervical carcinoma, which is quite a different thing and surely a much higher figure. In reading Danforth's paper I am a little confused as to just which figures he refers in some of his statistics. I have seen carcinoma develop in only one cervical stump in my private series of subtotal hysterectomies. I do not believe this represents more than one-tenth of 1 per cent of the cervices which I have left in. If a cervix is carefully inspected and biopsied when indicated before a decision is made to remove or retain it, the incidence of carcinoma can be held down to this figure.

Dr. Danforth makes the statement that "the man who requires over two hours for the performance of a subtotal operation had better not venture into the total field." With this I heartily agree but should like to broaden the statement in this way, "the man who requires over two hours for the performance of an average subtotal hysterectomy had better not venture into the field of pelvic surgery."

DR. N. SPROAT HEANEY, CHICAGO, ILL.—I have for years favored the complete removal of the uterus to the supravaginal operation for most of the patients coming under my attention. Earlier I left in more cervices than I do now. When I learned by experience how resistant to treatment an infection is, which occurs in the atrophied cervix left after a supravaginal hysterectomy, I left fewer and fewer cervices to annoy me and the patients in after years. Though in 100 cases of cancer of the cervix two or more may be in a cervical stump, this does not in any way mean that carcinoma occurs in 2 per cent of the cervical stumps left after 100 supravaginal hysterectomies. However small this incidence is, it is a danger avoided by the complete removal of the cervix.

Dr. Miller speaks of the cervix acting as a focus of infection for the production of an arthritis or other disease. I was raised in the institution which put focal infections "on the map." I am firmly convinced of the role of focal infections in the teeth and tonsils in the causation of affections in distant organs. Though I have had the question of the cervix in this regard constantly in my mind through all these years, I have yet to see a proved case. That a cervix, the seat of an acute gonorrhea, may cause gonorrheal rheumatism is true without question. I have also seen arthritis develop immediately after the intrauterine administration of radium and have seen the arthritis cured by the removal of the uterus with

its contained infected radium ulcer. With these two exceptions, I have never seen the cervix or the uterine body act as a focus of infection in the etiology of disease at a distance.

If the cervix requires any surgical attention at the time the uterus is to be removed, then the cervix should be removed at the same time. I believe that the cervix should never be cauterized either from above or from below at the time of the removal of the uterine body. The burning is too liable to cause a latent infection to become acute.

To my mind a conization should never be done either on the intact uterus or upon the uterine stump. This procedure should be completely eliminated from our list of operative resources.

It has been said that a vaginal hysterectomy leaves a shortened vagina. If the incision in the vagina is made at the same level as it would be made if doing a complete abdominal hysterectomy, then I cannot see why the route by which the uterus is removed can influence the length of the vagina. When a vaginal hysterectomy is done as part of the cure of a complete prolapse, then the vagina will be found to be short after the operation, for it was short before the operation, since a part of its length had been used in making up the breadth of the prolapse.

Since the attachments of the bladder to the uterus are the same whether the uterus is to be removed completely, vaginally, or abdominally, I cannot see why bladder difficulties should be commoner after vaginal hysterectomy than after abdominal hysterectomy, if the same perfection of technique is exercised.

From time to time I encounter a case where a combined abdominal and vaginal hysterectomy seems to be indicated. Where a cervix is very large, extensively torn or badly infected and the uterine body is too fixed to venture a vaginal hysterectomy, the cervix may be thoroughly cauterized and then removed as high as the uterine vessels. The vaginal vault may then be closed, a perineal repair, if needed, be done, and the abdomen entered for removal of the rest of the uterus. Where the pelvic tumor is so shaped or situated as to make the uterine vessels difficult of access from above, the combined operation may be done to very great advantage.

Since using ethylene gas, I have now completed 991 vaginal hysterectomies for benign disease of the uterus, with the same three deaths which have been previously reported in detail, with a mortality rate of approximately one-third of 1 per cent. I wish to congratulate Dr. Danforth on his having had no deaths in his series of 425 cases. I, too, have done almost 400 cases since my last fatal case.

Dr. Miller states that "although vaginal hysterectomy may be accomplished in almost any woman, it is not satisfactorily performed except where there is beginning prolapse of the uterus and a reasonable mobility of the structures." In the last 100 cases that I have done, the uterus was so large in 53 women that it had to be cut into two or more pieces to remove it. On the contrary, the uterus may be most easily removed in a nulliparous woman provided the vagina is not too tight, particularly if the vaginal vault is of normal proportions. If there is a little too much laxity of the vaginal walls they may fall together laterally and obscure the operative field. The easiest vaginal hysterectomy I ever did was on a 45-year-old virgin with an intact hymen and a small uterus full of tiny fibroids. A median incision of the hymen was made and the whole operation proceeded with the greatest of ease. There were 269 women in my series who were nulliparas.

DR. JAMES C. MASSON, ROCHESTER, MINN.—This subject is one in which I have been much interested for many years. In the five-year period from 1935 to 1939, inclusive, I have performed 1,277 hysterectomies. Of these, 888 were total hysterectomies with 6 deaths or a mortality rate of 0.67 per cent. One of these deaths should really not be charged to the hysterectomy, as the operation was done for tuboovarian abscesses and an apparently normal uterus was simply removed on account of the raw surface left after freeing up the inflammatory condition. Another death was due to pulmonary embolism. A third patient was a hunchback who died of atelectasis shortly after the operation.

In the series were 340 vaginal hysterectomies with one death. The probability is that this patient died of a ruptured appendix rather than anything resulting from the operation, but autopsy was refused.

There were 49 subtotal hysterectomies, with one death. In this case the woman weighed 260 pounds, had a huge ventral hernia and also multiple fibroids in the uterus. It was thought advisable to remove the uterus to help make room for the multiple coils of intestine that had been outside the abdomen for many years and replacing them markedly raised the intra-abdominal pressure.

I am absolutely in accord with both of the essayists that any one who is doing much pelvic surgery is keeping the best interest of the patient in mind by removing the cervix in most cases. It has not been at all uncommon in my experience to see a woman in the Clinic some time after a subtotal operation with a history of having had no leucorrhea until after the operation. Practically all of these patients are suspicious of cancer with a development of this kind.

The danger of cancer in the cervical stump, even if the number of cases is small, is appreciated by all. In the Clinic to date we have seen altogether 193 cases of cancer of the cervical stump left after subtotal abdominal hysterectomies, and we have seen about four times that many cases with cervicitis. In about 50 per cent of these cases, excision of the cervical stump was advised.

I agree with both essayists that until a satisfactory technique for the total abdominal hysterectomy is arrived at, the subtotal operation is a safer one, but I think that the Members of the Gynecological Society should be the ones to draw special attention to the fact that many of the subtotal operations which are being done today are not entirely satisfactory. My own experience is that thrombophlebitis, pulmonary embolism and other causes for morbidity and mortality are definitely higher following the subtotal operation. I think that this is due to the fact that an infection often results from cutting across infected glands in the cervix causing low-grade retroperitoneal inflammation with resulting thrombophlebitis or the development of a small abscess. This is especially true if hemostasis is not perfect in the operative field.

I agree with both Dr. Miller and Dr. Danforth that prolapse of the vaginal vault, shortening of the vagina and dyspareunia should not be charged to a total hysterectomy because all these conditions are due to faulty technique or failure to do satisfactory vaginal plastics at the same time.

One interesting point, that was suggested by my secretary, is that in my earlier experience, when I did a great many subtotals, the correspondence and repeated examinations were much more frequent than they are at the present time. In fact, there is no group of patients that seem so well satisfied and require so little care following surgery as those in which I have done total hysterectomies.

Among the subtotal hysterectomies that I am reporting there is one death two years later as a result of an obstruction. I operated upon another patient, fifteen years after she had had a pelvic operation elsewhere, in whom a loop of small bowel had become adhered in the pelvis. Just how many patients have obstruction or subacute obstruction or enough adhesions to have occasional gas pains, it would be hard to estimate. There is no doubt that many of the patients who have trouble following surgery in one hospital will go to another, or to another surgeon if they have complications. I am satisfied that following the subtotal operation, the leaving of an infected cervix, especially if the infected glands have been cut through, make a low-grade pelvic peritonitis much more likely, and adhesions are likely to form as a result.

Conization or cauterization after the subtotal operation is not a satisfactory protection against later malignancy and probably predisposes to local infection, as we leave a raw surface exposed to infection from the vaginal canal. When we consider that this is just beneath the peritoneum, it is reasonable to believe that there is often a little local peritonitis which would account for many of the adhesions deep in the pelvis.

DR. SIDNEY A. CHALFANT, PITTSBURGH, PA.—In the Pittsburgh hospitals for many years, it has been the practice to do the supravaginal hysterectomy in the great majority of cases. This, with the thorough cauterization of the cervix has been almost the routine procedure. At present Dr. Cashman has in process a study of all patients who have had a previous cauterization at Magee Hospital to determine the incidence of cancer after this procedure.

At Magee Hospital during the six years ending June, 1940, there were 976 hysterectomies by all operators with 18 deaths, or 1.84 per cent. The supravaginal operations predominated greatly, 874, with 14 deaths, or 1.6 per cent. The total abdominal hysterectomies numbered 54 with 2 deaths (3.73%); the vaginal hysterectomies, 48 with 2 deaths (4.17 per cent). The total abdominal operations were practically limited to cases of carcinoma of the fundus. During the same time on my personal service, there were 102 supravaginal operations with 1 death from peritonitis, and 6 total and 5 vaginal operations without mortality.

It is admitted that a competent gynecologist should be able to do the complete operation in the average case with no greater mortality or morbidity than the supravaginal operation. But there are many patients requiring hysterectomy in whom it is either (1) not necessary to do the complete operation, or (2) in whom it is more difficult and more dangerous.

The first class would include the fibroid case in the virgin who has no erosion of the cervix and who has had no opportunity for infection. There should be no postoperative leucorrhea as there has been none before the operation, and the incidence of cancer of the cervix in the nullipara is slight.

In the difficult class we would include particularly the fibroids associated with old inflammatory disease, where the uterus is firmly fixed in the pelvis and the dissection difficult. Here we do a thorough cauterization of the cervix and a supravaginal hysterectomy. The cauterization of the cervix must be sufficient to destroy all the epithelium in the canal and all the deep glands. Where this is done there is nothing left except a ring of fibrous tissue, the patient is free from leucorrhea, the vagina is not shortened, and the support adequate. There should be no more danger of developing carcinoma of the cervix than there is of a primary carcinoma of the vagina.

It is quite possible that we have been doing too few complete operations. But I am confident that in certain cases the incomplete operation is the safer procedure for the experienced gynecologist as well as for the occasional operator. Those who favor the complete operation are usually able to report just as good or *better* results from this as from the supravaginal hysterectomy. Is it possible that the latter group includes a larger percentage of the complicated cases in which one would naturally expect a greater mortality?

DR. LEWIS C. SCHEFFEY, PHILADELPHIA, PA.—I feel, as Dr. TeLinde and Dr. Chalfant do, that complete hysterectomy should not be routine for all cases. At Jefferson Hospital in Philadelphia we have followed a plan of thorough preliminary inspection of the cervix, and we cauterize nearly every case unless there is an absolutely intact cervix or when excessive hypertrophy, laceration, and eversion make complete hysterectomy seem more desirable.

About five years ago we followed up over 500 cases in which the cervix had been given proper attention and in those cases where that had not been done. Our incidence of carcinoma of the stump in these two groups was 0.5 per cent and 1.0 per cent, respectively. In about 400 cases of cervical carcinoma we have treated 18 cases of stump carcinoma, an incidence of 4.7 per cent. Our present feeling is that in women under 40 years there is a decided advantage in retaining the cervical stump in a healthy condition, or one which has been made healthy by cauterization, especially if it has been possible to conserve one or both ovaries. If we are dealing with a markedly diseased cervix and the patient is approaching, or is at the menopause or beyond it, then we believe in complete hysterectomy.

In certain instances complicating pelvic pathology and a debilitated patient make the complete operation much more hazardous than the subtotal procedure. To our mind, then, the question is not whether or not one is technically able to perform complete hysterectomy, but which procedure is better for the particular patient under consideration.

DR. DANFORTH (closing).—I would like to say in reply to Dr. TeLinde's remarks that I agree entirely with what he said about choosing the operation. Just before leaving home I did two subtotals, one on a virgin of 40 years who had an enormous fibroid and a perfectly healthy cervix. In the second case there was an involvement of the bowel in a bilateral carcinoma of the ovary, and I saw no reason for excising the cervix.

As to the statistics to which Dr. TeLinde referred, I think that he made a valid objection. The 2 per cent given by writers in the literature referred to the incidence of carcinoma of the stump in relation to all such stumps left in after the subtotal procedure. The larger figure merely indicates the percentage of carcinomas found in the retained stump in relation to all the cervical cancers seen in other clinics.

In my experience, after the usual type of vaginal hysterectomy which is done for nonmalignant bleeding or for small fibroids, the bladder usually gives little trouble. It is usual to have the woman urinating by the second day.

The question of carcinoma has been stressed rather unduly, to the neglect of the other conditions. Carcinoma of the stump does appear in some women but when the cervix becomes infected it is difficult to manage.

One point should be remembered about burns in extensive cauterization. A burn is the slowest healing type of wound there is. I have never been enthusiastic about cauterization of any type except the conservative cauterization which one does for the relief of leucorrhea. I have never been enthusiastic about cauterization at the time of operation.

THE EXCRETION OF ESTROGEN AND PREGNANEDIOL PRECEDING NORMAL PARTURITION*

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EVIDENCE supplied by animal experiments indicates that progesterone and estrogenic hormones play important roles in maintaining gestation, and probably also in determining the natural onset of labor.† It would seem reasonable to expect, therefore, that during the prepartal period significant fluctuations would occur in the urinary excretion of these hormones or their metabolic end-products. The data available from studies that have been made to date, however, are not entirely consistent; while they are in good agreement with respect to a few general features, no characteristic fluctuations or critical excretion-levels presaging the imminent approach of labor have been definitely established.[2-17]

Unfortunately, when these studies were made, not all of the methods of assay that were then available were sufficiently accurate to permit the demonstration of small but possibly significant fluctuations of excretion. While pregnanediol glucuronidate could be determined with reasonable accuracy by means of Venning and Browne's isolation procedure,[18] no equally reliable techniques of estrogen assay were at hand. Since fairly accurate colorimetric methods of assaying urinary estrogens have recently been developed in our laboratory, we have been interested in applying them to a further study of this problem. The present communication deals with the data obtained from a group of six patients.

METHODS

The patients selected for study were healthy young women of average physique and body weight. With one exception they were primigravidas. Their labors were spontaneous in onset and normal in character. Twenty-four-hour collections of urine were obtained from each patient twice weekly during the last three to nine weeks of gestation. These were analyzed for their content of estriol, estrone, estradiol, and pregnanediol.

Estrogen Determinations.—Our colorimetric procedure for the estimation of urinary estrogens has been described in detail elsewhere.[19] It is based upon the use of Kober's phenolsulfonic acid reagent, with which the natural estrogens form a characteristic pink color. The procedure differs from previously proposed colorimetric techniques[20-23] in that the urinary estrogens are purified sufficiently to yield with the color reagent

*Read by invitation, at the Sixty-Sixth Annual Meeting of the American Gynecological Society, Colorado Springs, Colo., May 26 to 28, 1941.

†The experimental literature, and the clinical implications thereof, have been admirably summarized by Reynolds.[1]

pigments closely resembling those obtained with crystalline hormones. This degree of purification is achieved without incurring serious losses of hormone. The method in its present form, however, is applicable only to pregnancy urine, wherein the ratio of impurities to estrogens is relatively low.

In the procedure, estriol is separated from the other estrogens and assayed directly. Since it is not feasible to effect a similar separation of the remaining estrogens, i.e., estrone and estradiol, without unduly complicating the procedure, these hormones are separated as a combined fraction and the latter then analyzed in the following manner: The sum of the two estrogens is determined by examining one aliquot of the fraction with the Kober reaction. A second aliquot is assayed with the ketosteroid reaction of Zimmermann.[24, 25] Since estrone, in contrast to estradiol, possesses a carbonyl group, this test should indicate the estrone content of our fractions. The difference between the two results is taken to represent the estradiol content. This obviously is based on the assumption that no additional unknown estrogen is present in these fractions.

With the use of these techniques, the estriol and estrone of pregnancy urine can be estimated within limits of error probably not exceeding 10 per cent. The indirect method employed for estimating estradiol involves larger errors, and only fair approximations of the quantities of this hormone are therefore obtainable. For estriol and estrone, however, the accuracy of the method exceeds, we believe, that of the biologic technique of assay. Moreover, the colorimetric technique is far less time-consuming, since it furnishes a complete quantitative assay of the urinary estrogens within two working days.

Pregnanediol Determinations.—Pregnanediol was determined by two methods: In one procedure, the technique of Venning and Browne[18] for the isolation of pregnanediol glucuronidate from unhydrolyzed urine was employed; the values thus obtained were multiplied by the factor 0.618 to permit their expression in terms of the free steroid. In the second procedure the recently proposed technique of Astwood and Jones[26] for the direct isolation of free pregnanediol from hydrolyzed urine was employed. Although there was a very satisfactory parallelism between the results obtained with the two methods, the values yielded by Astwood and Jones' method were consistently 20 to 40 per cent lower than those secured with the technique of Venning and Browne, the degrees of difference varying among the several patients but showing a characteristic constancy for each patient. Comparison of the results of recovery experiments with both procedures[15, 18, 26] indicates that the discrepancies are largely due to losses entailed in the hydrolysis necessary in the Astwood procedure. We, therefore, believe that the Venning procedure reflects more closely the total pregnanediol of the urine, provided no free steroid is present.*

*The nonhydrolyzed urine specimens, as used for the glucuronidate determinations, were periodically examined by Astwood's technique in order to determine whether any free pregnanediol was present. None, however, was found. We interpret this as evidence that the urine specimens were well preserved, and that the values obtained with the Venning procedure reflected the total amounts of preformed pregnanediol present.

Tabulation of Data.—Our findings have been recorded on charts, each of which summarizes the observations made upon an individual patient. The abscissas indicate the weeks of gestation during which the urine was examined and the maturity of pregnancy at the time labor began. Ordinates indicate the urinary output, in milligrams per twenty-four hours, of pregnanediol, estriol, estrone, and estradiol on the occasions indicated. In order to illustrate the widely varying amounts of the excretion of these substances with the use of a single scale of measurement, a logarithmic scale has been employed for the ordinate.

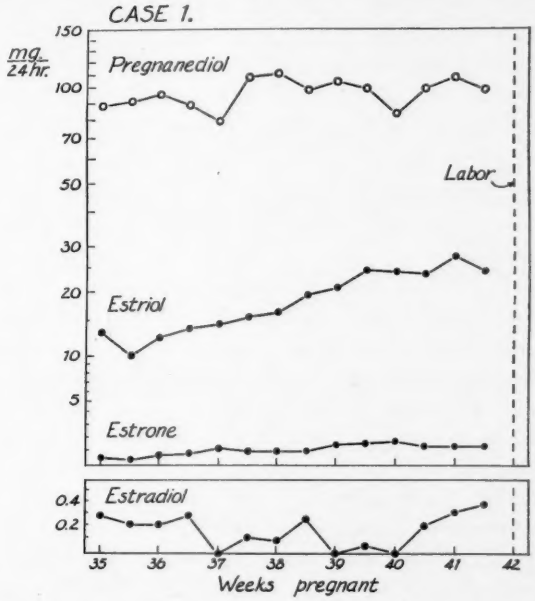

Fig. 1.—Urinary excretion of pregnanediol, estriol, estrone, and estradiol preceding parturition in Case 1. Excretions sampled at twice-weekly intervals during the last seven weeks of gestation. For interpretation of the data in this and the following figures, see the case protocols.

OBSERVATIONS

CASE 1.—Fig. 1 illustrates the excretion record of a secundigravida, aged 32 years, who gave birth to a 3,200 Gm. infant at the forty-second week of gestation following a labor lasting five hours. An outstanding feature of her record is the smooth character of the excretion-curves of estriol and estrone. The daily output of estriol rose steadily from a low point of about 10 mg. at the thirty-fifth week to a peak of 25 mg. just before labor. A rise in output of estrone ran parallel to this, though the peak of the daily excretion of this substance was less than 2 mg. The data relative to estradiol cannot readily be summarized; the unavoidable errors involved in the estimation of the extremely small excretions of this hormone undoubtedly account for some of the fluctuations seen in the figure, and permit us to say only that the hormone was present in the urine in appreciable amounts in the days immediately preceding labor. A daily average of about 100 mg. of pregnanediol was excreted during the last seven weeks of gestation; there was a slight upward tendency as term approached, with a peak level occurring at about the thirty-eighth week; temporary but probably significantly low levels were encountered at the thirty-seventh and fortieth weeks. It can be seen that any pre-labor trends in the

excretion of the different hormones were either constant or changed very gradually; it would be impossible, therefore, to forecast from either a single day's determinations, or from a series of consecutive determinations, the date on which labor would begin.

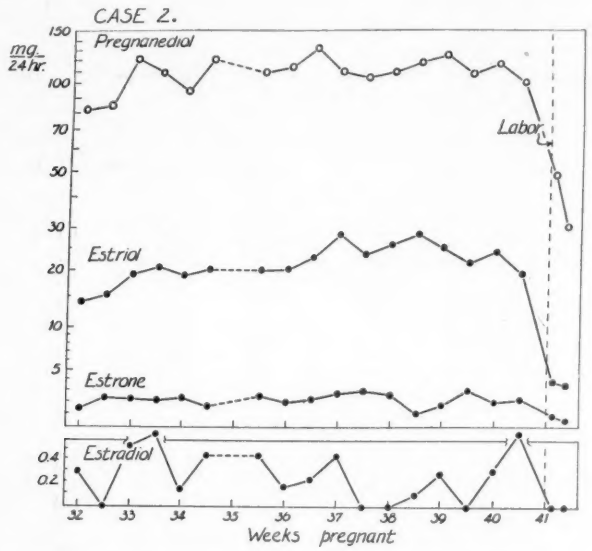

Fig. 2.—Urinary hormonal excretions during the last nine weeks of gestation, and the first two post-partum days, in Case 2.

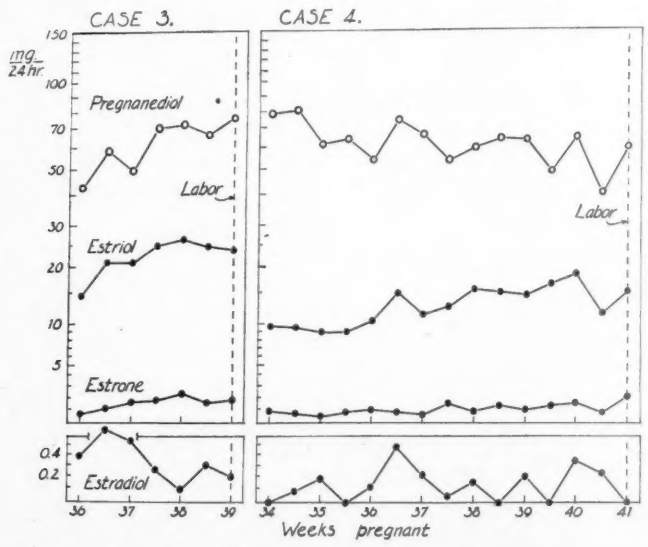

Fig. 3.—Urinary hormonal excretions in Cases 3 and 4. In these patients, the final urine samples were obtained within a few hours of the onset of labor.

CASE 2.—Fig. 2 summarizes the results obtained in this patient, a 20-year-old primigravida, who delivered a 3,000 Gm. fetus at the forty-first week, following a labor of sixteen hours' duration. The continuous curves of excretion in her record are not as smooth as in that of the previous patient. However, the levels and trends of all of the hormonal excretions shown in this figure resemble in a general way

those exhibited in Fig. 1. There was a higher daily output of estrone than in the first patient. It is noteworthy that the patient excreted relatively large amounts of pregnanediol as late as twenty-four hours following her delivery.

CASE 3.—This patient (see Fig. 3) was a 19-year-old primigravida who delivered a 3,100 Gm. infant at the thirty-ninth week, following a five-hour labor. Her excretion data resemble those of the first two patients, except that the output of pregnanediol was rising rather sharply when labor began, and the estradiol values were at a low level at that point.

CASE 4.—The data of this patient, also illustrated in Fig. 3, reveal further individual variations. This patient was a 17-year-old primigravida who delivered a 3,200 Gm. fetus at the forty-first week of gestation after a labor of nine hours' duration. While the trends and levels of the excretion of the estrogens were, in general, the same as those of the preceding patients, the trend of pregnanediol excretion was slowly downward during the last seven weeks of her pregnancy.

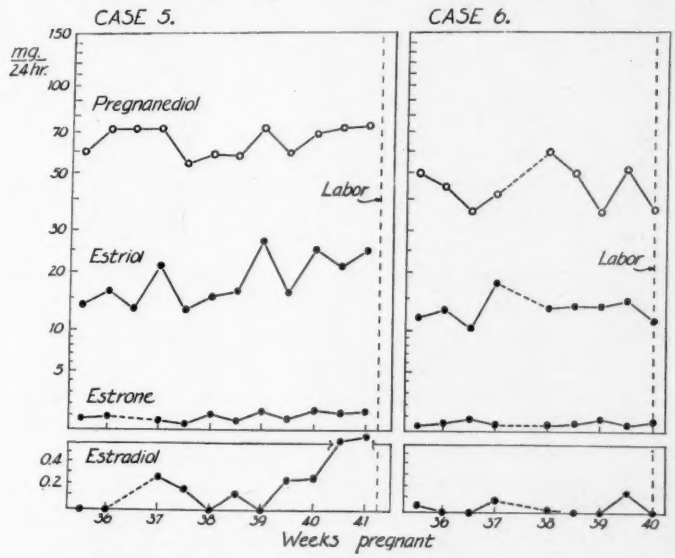

Fig. 4.—Urinary hormonal excretions in Cases 5 and 6.

CASE 5.—This patient was a 20-year-old primigravida who gave birth to a 3,100 Gm. infant at the forty-first week, following a thirteen-hour labor. Her record, illustrated in Fig. 4, may be viewed as an illustration of the difficulties of interpretation sometimes encountered in this type of investigation. It will be noted that while there is a general resemblance between her data and those of the first two patients, the excretion values obtained on successive occasions often varied markedly and without recognizable pattern. Since the values of all of the excreted products frequently fluctuated in the same direction, and tended to deviate with the volumes of the twenty-four-hour urine samples, we suspect that the patient was not always successful in obtaining accurate collections of her urine. Her record, however, shows a striking and unmistakable rise in output of estradiol in the four days preceding the onset of labor.

CASE 6.—This patient (see Fig. 4) was a 26-year-old primigravida, who gave birth to a 3,200 Gm. infant at the fortieth week after a labor of twelve hours' duration. Her health was normal throughout pregnancy except for a very unstable blood pressure, which tended to rise on frequent occasions to moderate hypertensive levels. Her hormonal excretions were so markedly below those of the

remaining patients, and the excretion trends so unique, that we have been at a loss to account for them except on the basis of her very mild medical disorder. Should further work justify such an interpretation, it would indicate that even minor medical disorders accompanying gestation may influence hormonal excretions profoundly.

COMMENT

The findings in this small series of patients corroborate, in a general manner, the results of the similar studies of Hain,[8, 9, 12] wherein the estrogens were estimated with biologic methods of assay. They indicate, apart from a pre-labor rise in excretion of estrogens, no constantly discernible correlations between hormonal excretion and the onset and course of normal parturition. Our experience is too limited to permit us to comment upon the observation made by several earlier workers[3, 6] that the rise in estrogen excretion which occurs during gestation is marked by transient cyclic fluctuations; it should be noted, however, that the cases we have so far investigated fail to show such fluctuations. It has been stated that estriol and estrone excretions fall off in amount just before labor begins, whereas the output of estradiol rises at that time;[3, 6, 11] our data offer some support for this suggestion. The observation of several workers that labor is preceded by a rise in the proportion of unconjugated urinary estrogens[2, 11] has not been investigated. With respect to pregnanediol, the data of the present study show no constancy; the pre-labor fall in output of this substance which we found in earlier investigations of both normal and toxemic patients[15-17] was not confirmed in the present series of patients. This clearly demonstrates that further work is necessary on both normal and abnormal patients before definite conclusions can be reached.* On the other hand, it seems clear at the moment that such studies are not likely to reveal sudden shifts in the prepartal excretions, or to show critical prepartal values, from either of which the clinician may hope to forecast the date or character of the oncoming labor.

Failure to demonstrate marked or sudden changes in hormonal excretion patterns at the end of gestation does not necessarily indicate that the hormones are not concerned in the processes which determine the onset and nature of labor. Currently available methods of investigation may fail to reveal the true nature of these excretion patterns, or the patterns may not reflect the rates of internal secretion and utilization of the hormones.

From the technical standpoint it may be said that it is not possible to effect complete hydrolysis of the conjugated estrogens of urine without causing their partial destruction. The hydrolysis procedures that have so far been proposed[27, 28] represent a compromise that gives optimal results with respect to total estrogen rather than to any individual substance. Although it is probable that future work in this direction will not materially alter the results obtained with present methods, such a study nevertheless seems desirable. Our convenient method of estrogen assay renders the prosecution of such a study more feasible than has heretofore been the case.

*The present series of patients forms the nucleus of a larger group now being studied in collaboration with Dr. Douglas Murphy, who is investigating the coincidental patterns of uterine motility in these patients with the use of the tocograph.

From the theoretical standpoint many explanations might be cited to show why urinary excretions may not reflect the quantitative aspects of the metabolism of hormones. The amounts of any hormonal excretion product recoverable from urine following the experimental administration of the parent substance represent, even under optimal conditions, only minor fractions of the quantities administered. Dingemanse and Laqueur[29] have shown that as much as 50 per cent of the total estrogen excreted under certain conditions may be put out in the feces. Also involved in this problem are questions of the sites and rates of utilization and destruction of the hormones, and the efficiency of conjugating and excretory mechanisms in the liver and kidneys. For the elucidation of many of these questions, the new colorimetric technique of estrogen assay should prove useful.

SUMMARY AND CONCLUSIONS

Frequent sampling of the urinary excretions of estrogen and pregnanediol during the last weeks of pregnancy was carried out in six healthy women, in order to determine whether any relations could be demonstrated between these excretions and the onset and character of the patients' labors. New and accurate colorimetric methods were employed for the estrogen analyses.

Apart from a gradual rise in output of estriol and estrone as term was approached, no constant patterns of hormonal excretion were observed. The rises in estrogen output were too gradual and the individual variations in the peak levels attained by different patients too marked, to make possible any forecast of the date on which labor would begin. Moreover, the variations in the maximal amounts of the hormones daily excreted by different patients did not appear to relate themselves to such clinical variables as the lengths of the labors or the weights of the infants and placentas.

Although further work is necessary, it appears that the roles which the estrogenic hormones and progesterone may play in the processes of parturition are hardly likely to be demonstrated by the rates at which these hormones or their metabolic end-products are excreted before parturition.

The author wishes to acknowledge his indebtedness and to express his thanks to his associates in the laboratory, Mrs. Dorothy Seymour Pettit and Mrs. Dorothy Leekley, for their valuable assistance in this investigation.

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EVALUATION OF COLORIMETRIC QUANTITATION OF 17-KETOSTEROIDS*

Application in Gynecology

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THE gynecic role of androgens has never been fully explained. During the past years various members of our group have accumulated data and made reports on the excretion of 17-ketosteroids under different conditions. In one of the first communications,[1] we stated our agreement with Korenchevsky[2] that it does not seem accidental that these substances are found in the female, and before the judicious employment of sex hormone preparations in gynecologic therapy is possible, an effort should be made to isolate and identify these hormones, the properties of these hormones alone and in combination with the female hormones be learned, their ratio established, and alterations during endocrine and gynecologic disturbances be ascertained. Subsequent reports,[3-9] especially by certain members of the group (E. C. H. and W. K. C.), have partially answered some of the questions and have advanced ideas as to the origin of the 17-ketosteroids.[3, 4, 8, 9]

This communication embraces the study of 216 women who had 5,700 twenty-four-hour specimens of urine quantified for 17-ketosteroids. According to various subjective and objective findings, the patients reported on were classified into 4 groups. The rationale of this grouping will be explained under each group. Significant information regarding the estrogen, progesterone, and androgen relationship seems desirable at this time, since there has been rather extensive use of androgens in the treatment of most functional conditions in women, for which previously estrogens have been reported to have been of value.

In selecting the patients for study, it would seem logical that varying degrees of ovarian failure would be most likely to reflect alterations in androgen and estrogen levels. Related information would be obtained by choosing patients showing virilizing symptoms.

METHODS OF STUDY

Consecutive twenty-four-hour specimens of urine were collected for estimation of 17-ketosteroids during the whole interval between menstrual flowings when feasible, and the report was the average of these individual values. The urine was refrigerated during the time of collection and until it was examined. Hydrolyses and extractions of the

*Read by Dr. Ross at the Sixty-sixth Annual Meeting of the American Gynecological Society, Colorado Springs, Colo., May 26 to 28, 1941.

Data taken from thesis submitted by W. Kenneth Cuyler in partial fulfillment of requirements for the Ph.D. degree in Duke University, 1941.

specimens were carried out by the technique of Cuyler and Baptist[10] which employed repeated washings of the extracts with alkali solutions to remove estrone, a 17-ketosteroid. The colorimetric estimations were done by the method of Oesting.[11] His method of calculation was employed and the amounts of 17-ketosteroids have been expressed in terms of international units of androsterone. These units may be converted into milligrams of crystalline androsterone by division by 10.

We recognize the fact that the data obtained do not interpret the bio-activity or chemical identity of the substances estimated.

As our previous communications have repeatedly pointed out, the values obtained by the method employed here have been consistently lower than most of the others reported, and comparison should be made with the excretion, as reported by us, in healthy women with normal ovarian function. This "yardstick" is based on the study of 13 normal women. The criteria for normalcy included: excellent general health; satisfactory general physical examination; absence of signs and symptoms of endocrinopathy; age range of 21 to 43 years; cyclic and quantitatively normal menses; normal urinary excretion of the pregnanediol-complex; and in most instances the association of well proliferated progestational endometriums with bleeding. Serious effort has been made to eliminate variables; one of us (E. C. H.) has interpreted all endometrial biopsy material, and one individual has made all of the colorimetric readings.

The average normal daily excretion ranged from the equivalent of 15 to 47 I.U. of androsterone.

All patients whose urinary titers were quantified had received routine medical, gynecologic, and endocrine surveys. All had metabolic rate determinations and roentgenograms of the sella turcica.

PRESENTATION OF DATA

A total of 216 women has been studied, with 5,700 twenty-four-hour urine specimens having been quantified for 17-ketosteroids. These figures represent all of the women patients studied. Those reported on here are only a fraction of this number.

Virilizing Syndrome.—To us at present, the chief interest of these observations on the excretionary values of 17-ketosteroids in hirsutism and virilizing syndromes lies in the fact that they concern patients in whom, by fact or by theory, the primary endocrine disturbance is hyperactivity of the adrenal cortex, and the secondary endocrine disturbance is hypofunction of the ovaries. These data, representing, therefore, potential measurements of varying degrees of primary hyperactivity of the adrenal, are to be compared with similar data submitted in the other groups in which the endocrine disturbance of patients is primarily ovarian. Also this comparison is for the purpose of testing a theory previously expressed by members of our group[3, 4, 8, 9] that a balance exists between estrogenic ovarian and androgenic adrenal functions which is upset by ovarian failure in the direction of increased adrenal activity. The data can serve as a valuable "measuring stick" as to the quantitative expectations in urinary 17-ketosteroids values when the adrenal cortex becomes hyperactive.

In this group (Fig. 1) there were 34 women who presented definite virilizing syndromes with obvious, and often masculine, hirsutism associated with secondary ovarian failure. The ages varied from seventeen to forty-eight years. According to their physical findings and symptomatology, they fell into 4 clinical groups: 3 patients with hirsutism and diabetes mellitus; 15 with hirsutism not associated with obvious endocrine disease; 13 patients with presumed adrenogenitalism; and 3 patients with adrenal cortical hyperplasia proved at operation. A total of 381 titers was run on these patients, an average of 11.2 titers per patient.

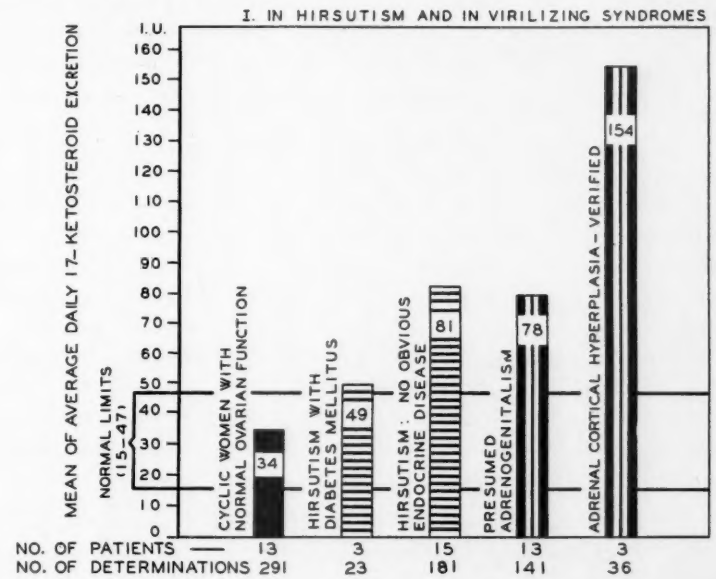

Fig. 1.—Urinary excretion of 17-ketosteroids in women with normal ovarian function and with ovarian failure. (The 17-ketosteroids were extracted by the method of Cuyler and Baptist and were estimated colorimetrically by the method of Oesting.)

Only 4 of these patients excreted quantities of 17-ketosteroids which fell within normal range. Fifty-nine per cent showed only moderate elevation of the titers. These ranged from the upper limits of normal to 100 per cent increases, or twice the normal limit. Of these 20 patients, 4 had titers which were increased only 20 per cent. Ten patients, or 20.5 per cent, excreted amounts more than twice that of the upper limits of normal, which ranged from 84 to 228 I.U., which was equivalent to 100 to 400 per cent increases. It is interesting to note that these data do not differ greatly from those obtained upon women being treated with intramuscular injections of testosterone propionate, doses varying from 10 to 25 mg. at intervals of two days. In such patients the excretion of 17-ketosteroids varied from 18 to 300 per cent over pretreatment levels. It is accepted generally that this type of treatment, if persistently carried out, will produce symptoms of virilism and hirsutism in the female. All of which suggest that the excretion values

do not differ greatly whether these symptoms be produced by injection or are spontaneous andromimetic responses. In our experience there has been a general tendency for the elevation of 17-ketosteroids to parallel the virilization or hirsutism; however, there were notable exceptions. As a rule, the patients with verified adrenal cortical hyperplasia yielded the highest titers. The three patients with diabetes associated with slight hirsutism had practically normal values. Others[12] have reported lowered levels in diabetes mellitus. The explanation probably lies in undernutrition and metabolic disturbances.

Menometrorrhagia.—Patients who experience too frequent or excessive uterine bleeding of functional origin may have diverse grades of ovarian failure. The grades of their ovarian disturbances can be gauged roughly by studies of endometrial biopsies taken at the onset of episodes of bleeding. Data from these studies as well as from a mass of clinical observations support the point of view that few of these

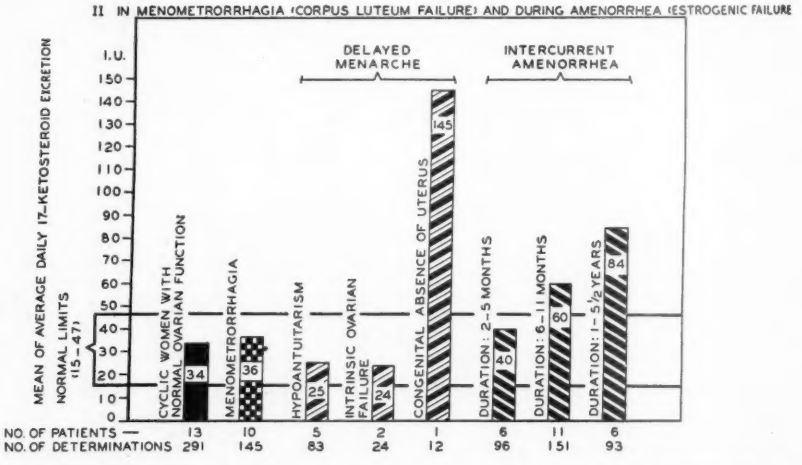

Fig. 2.—Urinary excretion of 17-ketosteroids in women with normal ovarian function and with ovarian failure. (The 17-ketosteroids were extracted by the method of Cuyler and Baptist and were estimated colorimetrically by the method of Oesting.)

patients exhibit any objective evidences of basic estrogenic deficiency, although intercurrent episodes of relative estrogenic deficiency obviously account for their menometrorrhagia.[4] As a rule, these individuals are well feminized, lack the endocrinopathic signs of glandular diseases, and are not possessed of hypoplastic sexual organs. Their ovarian disturbance concerns progesterone rather than the estrogens, being characterized by minimal or no corpus luteum activity. The proper selection of a group of patients with functional menometrorrhagia, characterized endocrinologically by deficiencies in corpus luteum function and not by any gross disturbances in estrogenic levels, permits study of the influence of simple corpus luteum failure of the ovaries upon the urinary excretion of 17-ketosteroids.

Ten women who presented the symptoms of excessive or too frequent uterine bleeding were studied. This was the only symptom of endocrine disease that was present. In none had therapeutic measures

been instituted. A total of 145 urine specimens were quantitated, which was an average of 14.5 per patient.

The urinary titers of all these patients fell within normal limits, with the exception of two whose daily average was 49 I.U., which is only 2 above the upper normal of 47 I.U. This is in line with previous observations[1, 4, 8, 13, 14] that there is no significant alteration in the titers of patients who have functional menometrorrhagia, which we interpret as indicating that no progestin : androgen ratio exists. It would seem that varying degrees of corpus luteum function, ranging from normal to the absence of progestin secretion (as indicated by biopsy examination of the endometrium and pregnanediol-complex estimates) in itself has no effect on the level of 17-ketosteroid excretion and implies that such a phenomenon is not followed by secondary activity of the adrenal cortex as measured by the excretion of these steroids.

Amenorrhea.—Amenorrhea when due to disturbed ovarian function is associated commonly with signs of estrogenic deficiency, among which are hypoplasias or regressions in the sexual system, including atrophic alterations in the endometrium and vaginal mucosa. These objective manifestations of estrogenic deficiency are evidenced as failures of sexual maturation in adolescent hypo-ovarianism, and as sexual regressions in intercurrent hypo-ovarianism of the adult. As a rule, in adult hypo-ovarianism, the degree of sexual regression increases with the duration of the amenorrhea. Patients with adolescent and adult hypo-ovarianism, as characterized by primary or secondary amenorrhea, present the opportunity of investigating the influences of primary and secondary estrogenic deficiencies upon the urinary excretion of 17-ketosteroids, i.e., the androgenic activity of the adrenals.

Thirty-one patients with amenorrhea were studied. Those with adolescent ovarian failure had roentgenologic evaluation of their osseous ages. A total of 459 determinations was made, an average of 14.8 per patient. A number had studies of the pregnanediol-complex, and the majority had serial endometrial biopsies studied as an index to ovarian failure. In certain instances subsequent clinical responses to therapeutic measures, especially to gonadotropins and thyroid substance, aided in determining the cause of ovarian failure. Of this group, 8 patients, ages ranging from 15 to 26 years, had primary amenorrhea related to hypoantuitarism, intrinsic hypo-ovarianism or, in one instance, faulty somatic development of the uterus. All of these patients, except the last mentioned, showed little or no evidence of sexual maturity.

Six of the 8 patients with delayed adolescence excreted 17-ketosteroids in amounts that were below normal while 2 were within normal range. This may be explained by the deficient somatic and sexual development, as were reported in preadolescence,[15] or it might mean that hyperactivity of the adrenal cortex occurs only after intercurrent adult or late failure of the ovary.

Twenty-three patients, aged from 16 to 38 years, had intercurrent amenorrhea lasting from two months to five and one-half years. Those whose amenorrhea lasted under six months were found, on occasions,

to excrete small amounts of pregnanediol-complex and in these few instances to have endometriums in estrogenic proliferation. Patients with intercurrent amenorrhea of greater than five months' duration consistently show increased urinary excretion of the 17-ketosteroids, while only one of the six patients whose amenorrhea had lasted from two to five months excreted more than normal amounts. The 17 patients, with only 3 exceptions, showed definite increase in their excretions. When considered together, there was an increase of 40 per cent in the patients with amenorrhea of one or more years' duration over those whose amenorrhea had lasted only from six to twelve months.

Climacteric.—Estrogenic ovarian failure, more severe in degree than that which occurs in many instances of intercurrent amenorrhea during the reproductive period, occurs physiologically during the sexual aging of woman or may be induced by radium or roentgenologic therapy. Complete ovarian deficiency occurs in bilaterally oophorectomized

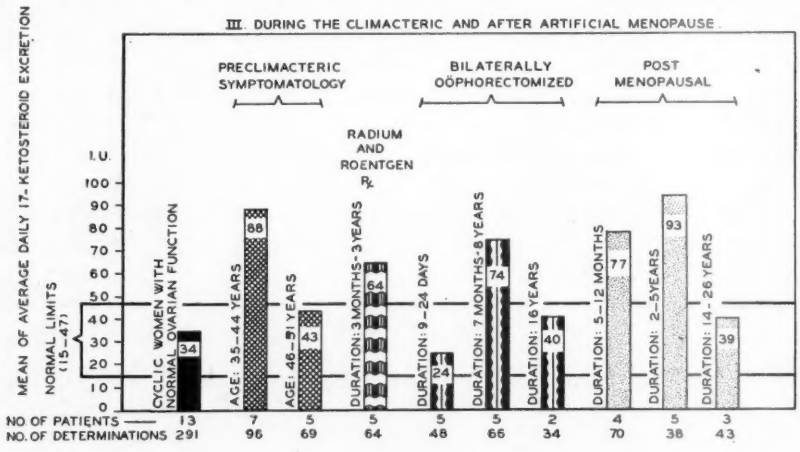

Fig. 3.—Urinary excretion of 17 ketosteroids in women with normal ovarian function and with ovarian failure. (The 17-ketosteroids were extracted by the method of Cuyler and Baptist and were estimated colorimetrically by the method of Oesting.)

women. In all of these instances, the causes of the failure may be reduced to a simple common denominator, intrinsic ovarian damage, resulting from senility, radium, roentgen ray, or surgery. Patients with this type of intrinsic ovarian failure afford an excellent opportunity for the investigation of possible alterations in the androgenic functions of the adrenals secondary to ovarian deficiency or deprivation. If the findings reported upon patients with amenorrhea were interpreted correctly, studies of 17-ketosteroids excretion during the climacteric and after artificial menopause should show similar, if not more marked, elevations to those during amenorrhea.

Forty-one women during the climacteric or after artificial menopause were studied. They were grouped according to the cause and degree of ovarian failure incidental to this state. A total of 528 determinations was made, an average of 12.9 per patient.

In Group I, there were 12 women between the ages of 35 and 51 years, none of whom had ceased to menstruate, who had symptoms that are generally recognized as due to spontaneous estrogenic deficiency associated with the menopause. The average daily titer of these patients was 36 to 121 I.U. with a mean average for the group of 69 I.U., which represents an increase of 50 per cent over the normal. It is interesting to note that the group from 35 to 44 years had a mean average of 88 I.U., while the mean average of the group from 46 to 51 years was 43 I.U. which places emphasis on age rather than the actual cessation of menses in the compensatory adrenal activity.

In Group II, there are 5 women who had had radium or x-ray therapy from three months to three years previously. The average daily titer was 49 I.U. which is consistent with our ideas of ovarian impairment following the use of such agents. It is difficult to judge with certainty when one can expect absolute hypo-ovarianism from these procedures.

In Group III, there were 12 women who had complete ovarian failure from previous bilateral oophorectomies. In order to get more exact information, they were further divided into 3 groups according to the time of operation.

Group A comprised 5 women whose operations had been done nine to twenty-four days before the time of the collection of the last twenty-four-hour specimen for study. Their daily average of excretion was 25 I.U.

Group B comprised 5 patients whose operations had been done seven months to eight years previously, and in these patients the daily titers were increased to an average of 74 I.U.

Group C comprised 2 patients whose operations had been done sixteen years previously, and both of these patients showed normal excretion value of 40.

In Group IV, there were 12 women who had had normal physiologic menopauses. They also are divided into three groups according to the length of time since the cessation of menstruation.

Group A comprised 4 women whose ages ranged from 42 to 49 years and whose elapsed time since menstruation was from five to twelve months. The excretion values in these women averaged 77 I.U., or 64 per cent increase.

Group B comprised 5 women whose ages ranged from 48 to 57 and whose elapsed time since menstruation was from two to five years. The excretion values averaged 93 I.U. or almost 100 per cent increase over upper limit of normal.

Group C comprised 3 women whose ages ranged from 62 to 74 years and whose elapsed time since menstruation was from fourteen to twenty-six years. The excretion values averaged 39 I.U., which was within normal range.

DISCUSSION

The androgenic substances obtained from the urine differ chemically from those obtained from endocrine glands, yet the three 17-ketosteroids: androsterone, dehydroisoandrosterone and the inactive etiocholanol-3-17-one occur in the urine of normal men and women. When

urine extracts are estimated for total 17-ketosteroids, both active 17-ketosteroids and those with low androgenicity are measured, while the biologic method tests and measures the specific hormonologic effect of the androgens. The excretion tends to be lower in women than in men.

Although there is evidence in experimental animals that the ovaries may supply androgens, certain clinical evidences point to the adrenals as the chief source in the human being. These facts strengthen this thought: normal men and women excrete qualitatively identical androgens in almost similar amounts; the level of excretion is apparently higher in some eunuchoids than in certain males, while in true eunuchs the amounts excreted are low, but within normal limits; oophorectomized women immediately after operation may excrete smaller amounts than the average, but again overlap the normal range; the excretion in Addison's disease is low, while in patients with adrenal tumors the amounts are high. These facts may be ascertained by grouping the observations and recorded data of many workers.

In a general way it may be said that the average daily 17-ketosteroid excretion, expressed in international units of androsterone, corresponds numerically to the chronologic ages up until sexual maturity.

An analysis of the data suggests the theory of ovarioadrenal reciprocities, which are influenced chiefly by way of the pituitary. During early life and until adolescence is well advanced, the adrenopituitary interchange is dominant in steroid metabolism. When primary or adolescent hypo-ovarianism occurs and is of sufficiently severe grade to result in failure of sexual maturation, this axis retains its dominant position even during adult years. Under these circumstances, the level of adrenal function remains about that characteristic of late preadolescence. Normally, however, with the advent of adolescence and the beginning of full ovarian function, the ovariopituitary interchange is superimposed upon the primordial adrenopituitary one. The result is a harmonious arrangement wherein the pituitary becomes conditioned to working with both adrenals and ovaries and to being influenced, as regards its functions, by the regulatory effects of the intrinsic steroids of both the ovaries and the adrenals. During the reproductive period, the ovary and pituitary come to dominate the endocrine system. When, however, ovarian failure occurs from pathologic or physiologic causes, the pituitary, accustomed to being balanced in function by both the adrenal and ovarian steroids, is released in part from its inhibitions and, thereby, becomes hyperactive, then the adrenal cortex is stimulated to secrete greater quantities of steroids. The now dominant adrenopituitary interchange is stronger because of its previous conditioning by the ovary and pituitary. Eventually, however, stabilization occurs from the inhibiting effects of the increased amounts of adrenal steroids upon the function of the pituitary. The result is that during the late stages of sexual aging and during somatic senescence, the adrenopituitary axis becomes stabilized and steroid output reaches normal levels.

Most of our attention in the past has been directed to the pituitary-ovarian relationship. Lately the role of the endometrium has been

appreciated, and now it seems orderly and proper that the adrenal must be considered as a more integral part of sex endocrinology.

In carrying out this method of 17-ketosteroid quantitation in this study, we have tried to evaluate its application as a test in gynecology. It would seem applicable as a method for grading various virilizing processes. In rare malignant tumors of the adrenal it should prove helpful.

We feel that the use of androgenic substances in gynecology are definitely limited[8] and would use this method as a further check on the progress of such therapy.

Finally it would seem that this method would aid in the prognostication as to the severity of ovarian failure.

SUMMARY

The urinary excretion of 17-ketosteroids was investigated in 34 women, whose ages ranged from 17 to 48 years and whose symptomatology of adrenal hyperactivity ranged from simple hirsutism of moderate degree to states of marked virilization. The values varied from normal to 400 per cent increases. These data are regarded as comparable to those obtained after repeated injections at two-day intervals of moderate doses (10 to 25 mg.) of testosterone propionate.

In 10 women, whose ages ranged from 16 to 38 years and whose common symptom was menometrorrhagia related to simple corpus luteum failure of the ovaries, the values for urinary 17-ketosteroids did not differ from those of healthy cyclic women with normal ovarian function. It is inferred from these studies that progesterone plays no active part in the gonadopituitary reciprocities, as evidenced by this excretion study.

Eight patients, aged from 15 to 26 years, with delayed menarches, and 23 patients, aged 16 to 38 years, with amenorrhea, due to intercurrent ovarian failure, of durations which ranged from two months to five and one-half years, were studied. The majority of these patients exhibited physical signs of estrogenic deficiency. There was no elevation of the 17-ketosteroid titers in the group of patients with delayed menarche, while definite elevations in the titers occurred in the patients with amenorrhea due to intercurrent ovarian failure which had lasted six months or more. A correlation apparently existed between the duration of the amenorrhea and the amount of 17-ketosteroid excretion. These findings indicate that late or intercurrent estrogenic ovarian failure precipitates androgenic hyperfunction of the adrenal cortex.

There were 41 patients studied during the climacteric and after artificial menopause, and they were divided into four groups of women: Group A, 12 women, aged 35 to 51 years, with ovarian failure presumably due to premenopausal stage of the climacteric; Group B, 5 women, aged 39 to 45 years, with amenorrhea of relatively short durations, related to previous radium or roentgenologic therapy; Group C, 12 women, aged 21 to 48 years, with complete hypo-ovarianism due to bilateral oophorectomies; and Group D, 12 women, aged 42 to 74 years, who had experienced physiologic menopause.

The majority of the patients of Group A excreted increased amounts of 17-ketosteroids. No definite increases in the urinary values of

17-ketosteroids were found in the patients of Group B. In Group C the urinary values of 17-ketosteroids were normal in women recently oophorectomized, i.e., nine to twenty-four days previously; these were increased definitely in women whose operations had been done from seven months to six years previously; and these titers were normal in 2 women, whose operations had occurred sixteen years previously. Quite similar findings were encountered in Group D: urinary titers of 17-ketosteroids were increased in those women whose menopause had occurred from five to twelve months and from two to five years previously, the latter group showing the higher values. In those women whose menopauses had occurred fourteen to twenty-six years previously the urinary titers of 17-ketosteroids were essentially normal.

The findings agree well with those of patients with amenorrhea due to intercurrent ovarian failure and are believed to support the thesis that adult estrogenic ovarian failure is followed by adrenal hyperactivity. Adrenal hyperactivity under these circumstances is considered to be an expression of the reciprocal arrangement between the adrenopituitary and ovariopituitary relationships which work through the pituitary. Theories based upon these reciprocities are applied to ovarian failure in general and to the hormonologies of the climacteric and somatic aging.

The application of this method of quantitation might be of value clinically in the following: as a test in rare malignant tumors of the adrenal and various virilizing syndromes; as a check in adrogenic therapy; as an aid in prognosing severe ovarian failure.

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602 WEST CHAPEL STREET

DISCUSSION ON PAPERS OF DRS. ROSS AND ASSOCIATES AND BACHMAN

DR. THOMAS KENNETH BROWN, ST. LOUIS, MO.—Cohen and Marrion found that both estrone and estriol were excreted in combined form, for the most part as esters of glucoronic acid. They observed striking variations in the partition of combined and free estrone and estriol just prior to the onset of labor. They found that labor was preceded or accompanied by a decrease in the total amount of estrogens, but an increase in the free forms of them.

Browne and Venning found that pregnanediol is excreted in relatively small amounts during the first two to three months of pregnancy and that its urinary titer decreased rapidly just prior to the onset of labor.

Through the kindness of Dr. Willard M. Allen, I should like to show two slides which illustrate the daily determinations of sodium pregnanediol glucuronidate pre-

ceding delivery in which a rather definite downward trend is indicated. The first is a case of toxemia and twins with bag induction, performed at a time when the titer was low; the second case a cardiac patient in whom induction was attempted three times before labor ensued and this occurred when a definite drop in titer was noted. These will be reported elsewhere shortly.

I should like to ask Dr. Bachman if it may not be necessary to obtain daily determinations in order to indicate when labor is imminent?

As yet we know but little about the role of androgens in the human organism. Why are they present in both male and female? Their presence may further indicate the delicate endocrine balance which is present in our patients and should warn us against upsetting this balance either by the injudicious administration of hormones or unnecessary operative procedures. It should be our aim to attempt to maintain conditions as nearly normal as possible.

It is suggested in Dr. Ross' paper that with the cessation of ovarian function the adrenals "take over" to a certain extent, but that this substitiute also begins to fail after some years. As yet Dr. Ross has not found the "Fountain of Youth" and the hope which might be expressed in the rise of androgen titer is probably "wishful thinking."

DR. HOWARD C. TAYLOR, JR., NEW YORK, N. Y.—Dr. Bachman's paper may be considered in two aspects: in the light of the new technical procedures he has developed, and in relation to the contribution it makes toward the theories of the causes of the onset of labor.

A colorimetric method for the determination of the estrogens has been one of the real needs in this type of investigative work for a long time. If, as Dr. Bachman has said, he has devised and used a method which has an error of only 10 per cent, it should be of tremendous value. This accuracy is probably greater than that usually obtained by methods of bio-assay unless very large numbers of animals are used. Besides the high degree of accuracy the method has the additional advantages of speed and economy.

A feature of interest in Dr. Bachman's curves is the consistency of the level of estriol excretion. Most previous studies and our own experience have led to the belief that there were wide daily fluctuations in the excretion rates of the estrogens during pregnancy. It seems possible at least that these fluctuations were only apparent and due simply to the chance inaccuracies of the older method of extraction and bio-assay. In the pregnanediol determinations also it is noteworthy that the quantities excreted from day to day are relatively constant. This again may be the result of a gradual improvement of a somewhat difficult technique.

As you know there is some physiologic evidence to suggest that progesterone causes relaxation of the uterus, whereas the estrogens are thought to increase its irritability. As a result of these observations, the onset of labor has been ascribed to a decreased progesterone and increased estrogen effect on the uterus. Dr. Bachman's figures, indicating no significant rise or fall in the excretion rate of either of these substances before the beginning of labor, are rather strong though not complete evidence against this view. Incidentally it casts some doubt on the clinical attempts to induce labor by the administration of estrogens. On the other hand, Dr. Brown, in discussion, has submitted a slide more acceptable to the traditional view that a fall in progesterone activity precedes the onset of labor. These contradictory findings are but another example of the difference in results which may be arrived at in two excellent laboratories employing these rather difficult technical procedures. More work must evidently be done to settle this particular point.

Dr. Ross has presented the results of 5,700 determinations of twenty-four-hour excretion of 17-ketosteroids and on the basis of these data has suggested certain additions to our basic knowledge of the relationships between gonads, adrenals, and the anterior pituitary gland.

As Dr. Ross has said, the so-called 17-ketosteroids are a mixture of chemically related substances probably produced principally in the adrenal. The actual figures for the twenty-four-hour excretion of 17-ketosteroids vary greatly, depending upon the method used. Dr. Ross, for example, reports a normal range of 15 to 47 international units of androsterone equivalent, using the Cuyler and Baptist hydrolysis and extraction technique and the Oesting colorimeter. Using the Callow technique and the Evelyn photoelectric colorimeter, we have normal figures of nearly

twice these values. As Dr. Ross has pointed out, investigations of this type must set up their own controls for the normal values.

As regards Dr. Ross' results a few comments may also be made:

a. The high values in the so-called virilizing syndrome are in accord with other reported observations.

b. The normal values in cases of menometrorrhagia are of considerable interest. The inference drawn from this finding that the corpus luteum plays no active part in the reciprocal relationships between gonads, anterior pituitary, and adrenal seems a step too far, however. The similarity of progesterone in its chemical structure to the other sex steroids and the apparent importance of the corpus luteum in controlling the duration of the sexual cycle makes it seem improbable to me that it has no effect on these glandular relationships.

Perhaps the most interesting of the observations are those showing a drop in 17-ketosteroid excretion immediately after castration, abnormally high values for some years thereafter, and finally a return to normal many years after the menopause. According to my understanding of Dr. Ross' paper, he suggests that in the presence of gonadal failure the adrenal becomes increasingly active and in a sense takes over the work of the ovary in balancing the anterior pituitary.

This seems to me a not unreasonable hypothetical explanation of the observed urinary findings. The absence of high 17-ketosteroids in primary ovarian failure seems perhaps to weaken the theory somewhat. There is no doubt, however, that the adrenal cortex plays an important part in the physiology of the sexual organs, and Dr. Ross' view on the exact nature of the adrenal's part in the sexual cycle is at least an interesting hypothesis to be worked on.

In general, certain reservations must be made in considering work based on the technique employed in these two presentations. Both the papers depend on the assumption that the excretion of the steroid hormones is somehow a measure of the functional activity of the glands from which they are derived. This is probably to some extent true, but limits must be placed on all inferences drawn from such data. Dr. Bachman has himself emphasized that the rates of urinary excretion of the steroid hormones do not depend only on the rate of their production, but are affected by utilization and destruction of the substances and by excretory mechanisms in the liver and kidney.

DR. SAMUEL H. GEIST, NEW YORK, N. Y.—Tests such as those employed by Dr. Ross in the measurement of urinary androgens have two purposes. One is simply to add to our physiologic knowledge. The second is to add to our armamentarium of therapeutic methods. Dr. Ross has indicated that definite amounts of hormonal substances are probably produced and excreted by every individual. One may infer that that substance has some physiologic value. It is probable also that the androgens have some therapeutic place in the treatment of the human female. I have been interested in that aspect of the androgen problem, but am perfectly willing to admit that our attempts have been mainly empirical. We have been advocating, however, the use of androgens in certain diseases.

The use of androgens in the female is still an experimental venture and simply because the literature reports good results in some cases, it does not by any means indicate that at the present time such substances should be used indiscriminately by the practitioner. If we will undertake our clinical investigations on that basis, we will make more modest claims and fewer mistakes. The future will decide the proper place of androgens in gynecologic disease.

DR. J. HOFBAUER, CINCINNATI, OHIO (by invitation).—In discussing the various factors which may be concerned in the onset of labor, postpituitary secretion should not be omitted. May I refer to my paper published in 1928, and also to a more recent report by Chang and Lin Noble. In their experiments, dogs' heads were perfused with Ringer's solution. Following the electrical stimulation of the vagus nerves, a considerable increase of pituitrin secretion ensued. This observation may have a definite bearing on the intensification of the Braxton Hicks' contractions during the last few weeks of pregnancy. In view of the fact that the uterus is supplied by both sympathetic and parasympathetic nerve fibers, it is reasonable to assume that the aforementioned uterine contractions may be responsible for augmented secretion of pituitrin which, in turn, registers its effect on the pregnant uterus.

THE EFFECT OF GONADOTROPINS UPON THE HUMAN OVARY*

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(From the Gynecological Service and the Laboratories of the Mount Sinai Hospital)

EVER since anterior pituitary gland and pregnancy urine extracts have been shown to exhibit gonadotropic activity in animals, gynecologists have been interested in determining whether similar effects could be produced in human beings. A potent gonadotropic substance would, for obvious reasons, be a valuable addition to the endocrine therapeutic armamentarium. Our interest in this subject goes back to 1933 when one of us (S. H. G.) reported the effects of chorionic gonadotropin upon the human ovary.[1] During the ensuing eight years, we have investigated the effects of a variety of gonadotropic substances upon the human ovaries, and in this communication we wish to present to you, briefly, the results of these studies.

All the available gonadotropic substances, viz., the gonadotropic factors derived from chorionic tissue, from the serum of pregnant mares and from the anterior lobe of the pituitary, were used singly and in several combinations. The effects of the gonadotropes upon the ovaries were studied with two questions in mind, viz., (a) can ovulation be induced in the human female by means of gonadotropin therapy? and (b) what histopathologic changes are produced by the gonadotropes?

METHODS AND MATERIALS

Ninety-one women, varying from 25 to 50 years of age, were selected for this study. Laparotomy was indicated in each instance, usually for uterine fibromyomas. The menses, in most cases, were quite regular, though several presented an irregular cycle or menometrorrhagia. Four women were gravid at the time of operation, and 3 were postmenopausal. The age grouping included 2 in the third decade of life, 37 in the fourth decade, 50 in the fifth decade, and 2 who were 50 years of age. Whenever possible, a variety of commercial preparations of a particular gonadotropin was used. The hypophyseal gonadotropin was employed in 34 cases; the chorionic, in 5 (previous report in 1933 by Geist included 50 cases); the equine, in 22; a combination of hypophyseal and chorionic, in 5; a combination of hypophyseal and equine, in 9; a combination of chorionic and equine, in 10; and a combination of chorionic and stilbestrol, in 6. Whenever feasible, a preliminary endometrial biopsy, vaginal biopsy, and endometrial smear were taken for comparison with the posttherapy effects. Injections were given over one to several days, in varying doses as described in detail below

*Read, by Dr. Geist, at the Sixty-Sixth Annual Meeting of the American Gynecological Society, Colorado Springs, Colo., May 26 to 28, 1941.

(Tables I to VII). The gonadotropic hormone was administered at different times in the menstrual cycle to ascertain any change in ovarian response before, during, or after the occurrence of spontaneous ovulation. At operation, the ovaries were carefully inspected, particularly for evidence of recent stigmas of ovulation. Both ovaries were removed whenever possible. In younger individuals, a unilateral oophorectomy was performed and a segment taken of the contralateral ovary. Appropriate sections of the endometrium were cut and fixed immediately for correlation with the ovarian findings. Several cross sections were made of each ovary and representative portions stained for microscopic examination. In the latter part of this investigation, sufficient sections were examined to include all the cystic follicle structures that could be visualized grossly. In analyzing our results, consideration was taken of the patient's age, the dosage of the gonadotropin, the time in the menstrual cycle during which injections were given, the time of operation, and the relationship of the endometrial to the ovarian findings.

CRITERIA IN THE EVALUATION OF ARTIFICIALLY INDUCED OVULATION

The divergence of opinion regarding the ovarian reaction to gonadotropin administration reported in the literature has impressed us with the necessity for a standardization of the histologic criteria of an induced ovulation and its differentiation from spontaneous ovulation. This differentiation is of paramount importance since the test animal (the human female), in these experiments, ovulates spontaneously. It is important, therefore, in each instance, to make certain that the evidence of ovulation which may be found after gonadotropin administration is not a normal, spontaneous phenomenon. Gross estimation of the number of corpora lutea within an ovary is unsatisfactory, since even microscopically it may be difficult to judge the age of a corpus luteum. The state of the endometrium may be helpful, since it responds to cyclical changes in hormonic ovarian function. Although it is conceded that the endometrium occasionally does not accurately reflect the *level* of ovarian hormonal function[2-4] and that the effects of a *very recent* ovulation may not be conspicuous in the endometrium, a mature, current corpus luteum may be expected to cause secretory endometrial changes. Aside from the histologic details of a recently ruptured Graafian follicle, some of the criteria we have attempted to follow in judging an artificially induced ovulation include the following:

In those women who menstruate at regular four-week intervals, it may be assumed that ovulation normally occurs during the midinterval, roughly between the tenth and sixteenth days. If, following gonadotropic therapy, the ovaries are removed during the ovulatory stage and present a single, recently ruptured follicle or very early corpus luteum, such a finding cannot be regarded as a result of medication, since this may have been, and probably was, a normal, physiologic occurrence. If operation is performed during the postovulatory phase, the result can be considered positive only if, in addition to a current corpus luteum, a freshly ruptured follicle is found. When the ovaries are removed during the preovulatory period, a ruptured follicle must have occurred

sufficiently early to remove all doubt of a coincident, short menstrual cycle, before it can be deemed a positive result. Furthermore, in women with irregular menses or metrorrhagia, in whom the time of spontaneous ovulation is uncertain, definite conclusions cannot be drawn if only a single, recently ruptured follicle is found, without an accompanying current corpus luteum and secretory endometrium.

CRITERIA IN EVALUATING HISTOLOGIC OVARIAN CHANGES

A major difficulty in reporting histologic changes in the follicular system of the human ovary has been the lack of data on what constitutes the normal variations, both qualitatively and quantitatively. This is understandable because (a) individual variations are marked; (b) the follicular system is constantly undergoing physiologic changes; and (c) there is no uniformity of response throughout the ovary. Accordingly, 25 untreated patients were examined to establish a basis of comparison. Many sections of each ovary were made, to include all cystic follicle structures. The number of cystic follicles were found to be so varied that a mean average, though satisfactory statistically, would be of no great practical value. The presence, in the treated cases, therefore, of more than the average number of follicles, cannot be considered a definite indication of stimulation by the administered gonadotropin. However, an especially large number of follicle cysts was recorded as an increase. The control ovaries were particularly of aid in furnishing a basis of comparison for estimating the extent of granulosa cell activity, theca cell proliferation and theca interna luteinization.

RESULTS

Chorionic Gonadotropin.—Geist,[1] in 1933, studied the microscopic effects of antuitrin-S on the ovaries of 50 normally menstruating women. The dosage employed at that time was small (600 to 2,200 R.U.), and administered subcutaneously, over periods of thirty-six to one hundred hours. Though some changes were noted in the majority of cases, they could not be considered of unusual significance. The observations of Ross[5] and Hamblen[6] appear to be in substantial agreement with those of Geist. Zondek[7] noted cystic alterations of the follicles following the use of pregnancy urine gonadotropes, and with extremely large doses (26,500 R. U.), observed the presence of 4 corpora lutea in an enlarged ovary of a 30-year-old woman. Mandelstamm and Tschaikowsky[8] found degenerative changes in maturing follicles, an increase in the number of follicle cysts and numerous corpora lutea. Westman[9] also found recent corpora lutea as well as cystic follicles and hemorrhagic areas in the ovaries of 3 patients who had received 3,600 to 5,000 R.U.

To complete our observations on the ovarian histopathology induced by the chorionic gonadotropins, large doses of A.P.L. (Ayerst, McKenna and Harrison, 500 to 25,000 R.U.) were administered intramuscularly, over periods of two to five days, in 5 women varying in age from 34 to 49 years (Table I). The ovarian response could be summarized as follows:

There was no evidence of artificially stimulated ovulation (Table I). An active corpus luteum, when present, could in all instances be cor-

TABLE I. EFFECTS OF CHORIONIC GONADOTROPINS UPON OVULATION IN THE HUMAN BEING

NO.	AGE	MENSTRUAL INTERVAL	CHORIONIC GONADOTROPIN GIVEN INTRAMUSCULARLY	NO. OF RAT UNITS	INJECTION DAY OF CYCLE	OPERATION DAY OF CYCLE	ENDOMETRIUM	CURRENT C.L. OR EARLY CURRENT RUPTURED FOLLICLE (C.R.F.)	INDUCED OVULATION
1	43	25-26	A.P.L.	4,000	16-17	18	Secretory	+ (double)	0
2	34	28	A.P.L.	500	11-15	16	Secretory	+	0
3	49	Post-menop.	A.P.L.	1,500	--	--	Hypoplasia	0	0
4	46	28	A.P.L.	25,000	28-32	33	Secretory	+ (double)	0
5	40	28	A.P.L.	25,000	32-36	37	Secretory	+ (double)	0

related with the postovulatory phase of the menstrual cycle and with secretory effects in the uterine endometrium. In 3 instances, a double corpus luteum was found. This high incidence could not be interpreted as other than an unusual coincidence, since the corpora lutea were identical in all respects, mature in development and more advanced than any follicle that could have been caused to rupture artificially during the few days preceding operation. Unless the time of oophorectomy is postponed several days beyond the period of stimulation by the gonadotropic hormone, only a recently ruptured follicle or very early corpus luteum can be expected to be the result of an induced ovulation.

Hypophyseal Gonadotropin.—The hypophyseal gonadotropins were administered to 34 patients varying in age from 32 to 50 years. Gonadotropic factor (Ayerst, McKenna and Harrison) was injected intramuscularly in doses of 350 to 16,500 R.U., over periods of one to ten days, while antuitrin (Squibb) was given in amounts of 275 to 4,250 R.U., over a period of three to seven days. The time in the menstrual cycle during which injections were given was sufficiently varied to include every possible phase.

The ovarian effects are tabulated in Table II. In no instance, despite extremely large doses in some cases, was ovulation induced. In 2 cases (Cases 4 and 14), double or twin corpora lutea were found. These were identical in appearance and of the same degree of maturity. Their occurrence in the postovulatory period and their development in relation to the time of the injections, permitted only the diagnosis of normal, current, twin ovulations.

Definite and sometimes conspicuous histologic changes were noted in a majority of the ovaries studied. Differences in age, duration of therapy, and the phase of the cycle in which the gonadotropin was used could not be correlated with the degree of ovarian change. In a general way, however, where larger doses were employed, more profound histologic effects were obtained.

No positive statements can be made as to any absolute increase in the number of cystic follicles. In a few instances only, there seemed to be an apparent increase. In approximately 25 per cent of the cases, the ovaries contained cystic follicles which were larger than the average, with increased production of follicular fluid. In half the cases, there

TABLE II. EFFECTS OF HYPOPHYSEAL GONADOTROPINS UPON OVULATION IN THE HUMAN BEING

NO.	AGE	MENSTRUAL INTERVAL	HYPOPHYSEAL GONADOTROPINS GIVEN INTRAMUSCULARLY	NO. OF RAT UNITS	INJECTION DAY OF CYCLE	OPERATION DAY OF CYCLE	ENDOMETRIUM	CURRENT C.L. OR EARLY CURRENT RUPTURED FOLLICLE (C.R.F.)	INDUCED OVULATION
1	38	38	Gonad. Factor	16,500	22-4	6	--------	0	0
2	47	30	Gonad. Factor	4,500	14-17	18	Secretory	+	0
3	41	28	Gonad. Factor	3,000	18-19	28	Secretory	+	0
4	43	28	Gonad. Factor	1,500	15	19	Secretory	+ (double)	0
5	44	Menomet.	Gonad. Factor	9,000	33-35	36	Late Prolif.	+	0
6	46	28-35	Gonad. Factor	6,000	27-28	31	--------	0	0
7	32	28	Gonad. Factor	3,000	8-9	12	Secretory	+	0
8	36	28	Gonad. Factor	12,000	27-6	8	Proliferative	0	0
9	39	28	Gonad. Factor	6,000	Gravid 60	65	Decidua	+	0
10	37	31	Gonad. Factor	4,500	9-11	15	--------	0	0
11	44	28	Gonad. Factor	9,000	Gravid 60	124	Decidua	+	0
12	50	Postmenop.	Gonad. Factor	6,000	--	--	Hypoplasia	0	0
13	40	Irreg.	Gonad. Factor	4,500	18-20	22	Secretory	+	0
14	35	26	Gonad. Factor	9,600	17-21	23	Secretory	+ (double)	0
15	43	28	Gonad. Factor	6,600	26-28	29	Proliferative	0	0
16	43	28	Gonad. Factor	350	5-6	8	--------	0	0
17	45	23-25	Gonad. Factor	1,500	7-9	10	Proliferative	C.R.F.	0
18	37	28	Gonad. Factor	750	20-23	24	Secretory	+	0
19	42	28	Gonad. Factor	2,250	26-7	8	Proliferative	0	0
20	37	28	Gonad. Factor	1,600	26-4	5	Proliferative	0	0
21	40	28	Gonad. Factor	1,700	21-27	28	Secretory	+	0
22	38	Menomet.	Gonad. Factor	2,200	20-3	7	--------	0	0
23	40	28-30	Antuitrin	275	8-11	12	Proliferative	0	0
24	43	25	Antuitrin	750	19-23	24	Proliferative	0	0
25	38	28	Antuitrin	2,250	10-17	18	Proliferative	0	0
26	36	21	Antuitrin	1,000			Proliferative	0	0
27	39	28	Antuitrin	1,750	8-12	13	Proliferative	0	0
28	48	Menomet.	Antuitrin	4,250	--	--	Proliferative	0	0
29	40	28	Antuitrin	1,250	--	--	Late Prolif.	Early C.L.	0
30	46	21	Antuitrin	1,250	11-14	16	--------	0	0
31	48	27	Antuitrin	1,250	27, 1-4	5	Proliferative	0	0
32	37	21-28	Antuitrin	2,000	26-30	31	Proliferative	0	0
33	45	28	Antuitrin	500	5-7	8	Menstrual	+	0
34	42	Gravid	Antuitrin	2,500	--	--	Decidua	+	0

was evidence of a stimulated growth of granulosa cells lining the cystic follicles, and of the theca interna cells about them, with partial luteinization of the latter.

The follicle cysts were not uniform in appearance, some showing greater stimulation than others. Cystic follicles that had apparently progressed to an advanced state of atresia seemingly did not respond to hypophyseal gonadotropin stimulation. Others presented a granulosa cell lining of variable thickness but uniform cellular activity, similar to that seen in maturing follicles, except for the significant fact that they did not contain any ova. Another finding which merits particular attention was the presence of cystic follicles in which one portion of the wall was composed of a thickened layer of well-developed granulosa cells with mitotic figures, while another portion of the same follicle consisted merely of a flattened layer of inactive cells. Some of the follicle cysts were slightly convoluted in outline, with evidence of granulosa cell proliferation, and theca cell growth with conspicuous luteinization. These at first strongly suggested the histologic picture of a recently ruptured follicle except, however, that they were unruptured. Close scrutiny of numerous cross sections of the ovary containing one or more of the stimulated cystic follicles did not reveal the presence of ova or the degenerative remnants of ova within their walls. This fact along with the absence of growing follicles beyond that seen normally seems to point to the conclusion that *while the hypophyseal gonadotropin in the human female may stimulate those granulosa cells and theca interna cells in follicles undergoing atresia, which are still capable of response, it apparently does not induce follicular maturation.* In addition to increased size and follicular fluid content of the cystic follicles, granulosa cell and theca interna cell stimulation, fully half the cases presented evidence of perifollicular congestion and hemorrhage, similar to that seen following chorionic gonadotropin.

Equine Gonadotropin.—Reports by Watson, Smith, and Kurzrok,[10] Moricard and Saulnier,[11] Siegmund,[12] and Westman[9] have indicated that follicle stimulation could be obtained in the human ovary with equine gonadotropin, but that ovulation with resultant corpus luteum formation did not follow. Ross[5] and Hamblen[6] have likewise been unsuccessful in producing ovulation with the mare serum gonadotropin. Hartman,[13, 14] working with adult monkeys, found a reasonable certainty of stimulated ovulation in only 7 of 104 cases. In 1938, Davis and Koff[15] reported single and multiple induced ovulation in women with the mare serum gonadotropin administered intravenously. To date, this work has been confirmed only by Siegler and Fein, who reported artificial ovulation in 16 of 30 women.[16]

Gonadogen (Upjohn), gonadin (Cutter) and anteron (Schering) were administered intravenously or intramuscularly in 22 women varying in age from 30 to 46 years. In no instance was conclusive evidence of artificially induced ovulation found (Table III).

Of the 22 patients receiving equine gonadotropins, fully half presented ovaries that showed evidence of slight to moderate perifollicular hemorrhage and congestion (Fig. 1). Only a few gave indications of conspicuous cystic follicle enlargement, stimulation of the granulosa cells, or increased theca interna cell activity. The histologic ovarian changes may, therefore, be considered as differing only quantitatively from those induced by the other gonadotropins.

TABLE III. EFFECTS OF GONADOTROPINS DERIVED FROM THE SERUM OF PREGNANT MARES UPON OVULATION IN THE HUMAN BEING

NO.	AGE	MENSTRUAL INTERVAL	EQUINE SERUM GONADOTROPIN	NO. OF UNITS	ROUTE*	INJECTION DAY OF CYCLE	OPERATION DAY OF CYCLE	ENDOMETRIUM	CURRENT C.L. OR EARLY CURRENT RUPTURED FOLLICLE (C.R.F.)	INDUCED OVULATION
1	37	28	Gonadogen†	60	IV	16	17	Secretory	+	0
2	39	28	Gonadogen	60	IV	21	22	Adv. Prolif.	0	0
3	46	28-35	Gonadogen	60	IV	23	24	Hyperplasia	0	0
4	35	28-30	Gonadogen	60	IV	13	14	--------	C.R.F.	0
5	39	28	Gonadogen	60	IV	22	23	Secretory	+	0
6	42	Menomet.	Gonadogen	60	IV	?	1	Proliferative	0	0
7	45	Menomet.	Gonadogen	60	IV	28	30	Adv. Prolif.	0	0
8	39	28	Gonadogen	90	IV	18	19	Secretory	+	0
9	45	30	Gonadogen	120	IV	20	21	Adv. Prolif.	C.R.F.	0
10	44	28	Gonadogen	120	IV	9-10	11	Early Secr.	+	0
11	42	28	Gonadogen	150	IV	12	13	Adv. Prolif.	+	0
12	32	28	Gonadogen	180	IV	12-15	16	Secretory	+	0
13	32	26-28	Anteron‡	350	IM	9-15	16	Secretory	+	0
14	40	25-30	Anteron	500	IM	22-27	27	Late Prolif.	0	0
15	41	28	Anteron	500	IM	13-16	17	Secretory	+	0
16	39	26-28	Anteron	700	IM	1-6	11	Late Prolif.	C.R.F.	0
17	39	Menomet.	Gonadin§	1,200	IM	28-29	32	Secretory	+	0
18	37	Irreg.	Gonadin	2,400	IM	1-5	6	Proliferative	0	0
19	41	28	Gonadin	3,600	IM	10-15	16	Secretory	+	0
20	38	Irreg.	Gonadin	600	IM	28	34	Late Prolif.	0	0
			Gonadogen	60	IV	29-31				
21	30	28	Gonadogen	30	IV	22-24	26	--------	+	0
			Gonadin	1,000	IM	25				
22	37	Irreg.	Gonadin	3,000	IM	26-30	34	Late Prolif.	C.R.F.	0
			Gonadogen	60	IV	30-32				

*IV, Intravenously; IM, intramuscularly.
†Cartland-Nelson units.
‡International units.
§Cole-Saunders units.

TABLE IV. EFFECTS OF A COMBINATION OF HYPOPHYSEAL AND CHORIONIC GONADOTROPINS UPON OVULATION IN THE HUMAN BEING

NO.	AGE	MENSTRUAL INTERVAL	HYPOPHYSEAL AND CHORIONIC GONADOTROPINS GIVEN INTRAMUSCULARLY	NO. OF RAT UNITS	INJECTION DAY OF CYCLE	OPERATION DAY OF CYCLE	ENDOMETRIUM	CURRENT C.L. OR EARLY CURRENT RUPTURED FOLLICLE (C.R.F.)	INDUCED OVULATION
1	48	28	Gonad. Factor* A.P.L.	7,500 12,500	14-18 19-21	22	Proliferative	0	0
2	42	28	Gonad. Factor* A.P.L.	6,000 17,500	17-20 21-25	26	Secretory	+	+
3	43	26-27	Gonad. Factor* A.P.L.	4,500 5,000	2-4 5-6	7	Hyperplasia	0	0
4	25	28	Gonad. Factor* A.P.L.	10,500 17,500	23-28	29	Secretory	+	0
5	29	30	Gonad. Factor* A.P.L.	7,500 12,500	29-33	34	Secretory	+	0

*Collip.

COMBINATION GONADOTROPIN THERAPY

The experimental studies of Leonard,[17] Evans and his co-workers,[18, 19] Engle and Hamburger,[21] and Mazer and Katz[20] have shown that hypophyseal gonadotropin administered with the chorionic hormone has a

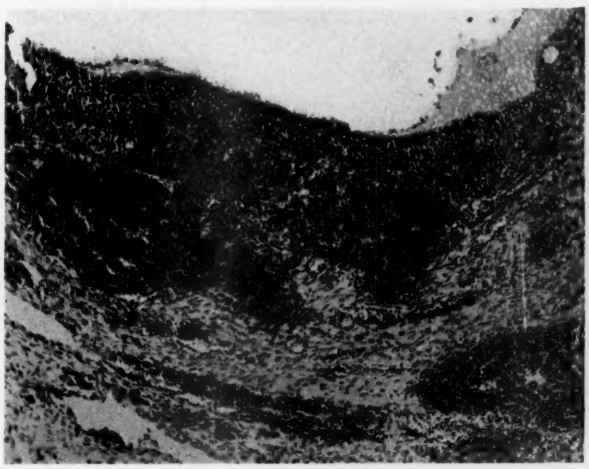

Fig. 1.—Case 12 (Table III, Path. No. 66213), aged 32, had normal menstrual cycle. One hundred and eighty units of gonadogen were given intravenously on the twelfth to fifteenth day of the cycle. Operation was performed on the sixteenth day of the cycle. Section shows the most frequent effect noted after equine serum therapy, viz., perifollicular congestion and hemorrhage.

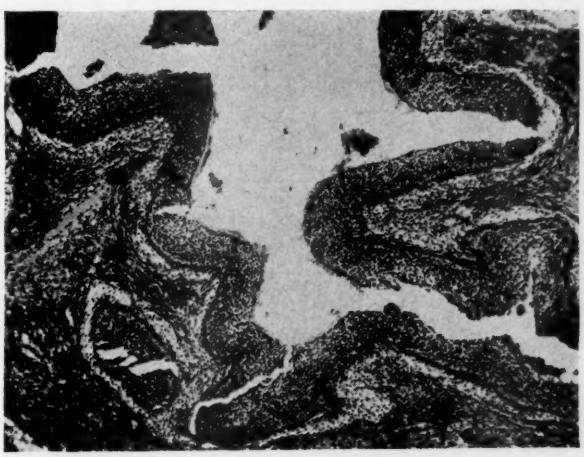

Fig. 2.—Case 10 (Table II, Path. No. 65301), aged 37, had menstrual interval of 31 days. Forty-five hundred R. U. of hypophyseal gonadotropic factor (Collip) were given intramuscularly on the ninth to eleventh day of cycle. Ovaries were removed on the fifteenth day. The follicle wall shows a serpiginous outline, without rupture. Such a picture may be easily confused with that seen soon after the rupture of a normal Graafian follicle.

synergistic effect. Recently, Mazer and Ravetz[23] have reported "stimulation and overstimulation of the ovaries in 20 of 23 patients" treated with a combination of hypophyseal and chorionic gonadotropins.

Combination of Hypophyseal ("Synergist") and Chorionic Gonadotropins.—Five women, 25 to 48 years of age, received both hypophyseal and chorionic gonadotropins together or in succession, in either the pre- or postovulatory phases of the menstrual cycle. One case (Table IV,

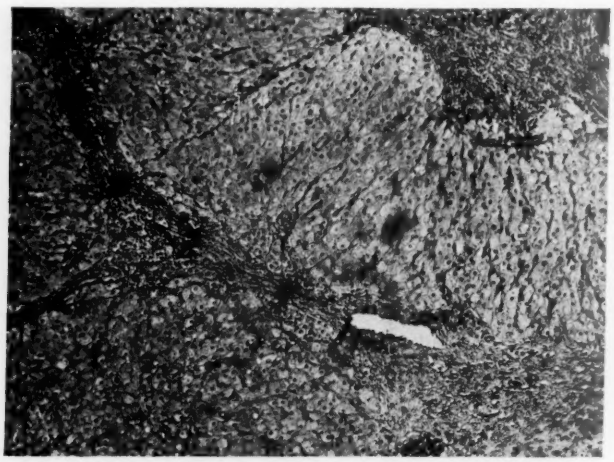

Fig. 3*A*.—Case 2 (Table IV, Path. No. 66457), aged 42, had a normal menstrual cycle. Six thousand R.U. of gonadotropic factor and 17,500 R.U. of A.P.L. were given during the seventeenth to the twenty-fifth day of the cycle. Operation was performed on the twenty-sixth day. Section shows normal, active corpus luteum of current cycle.

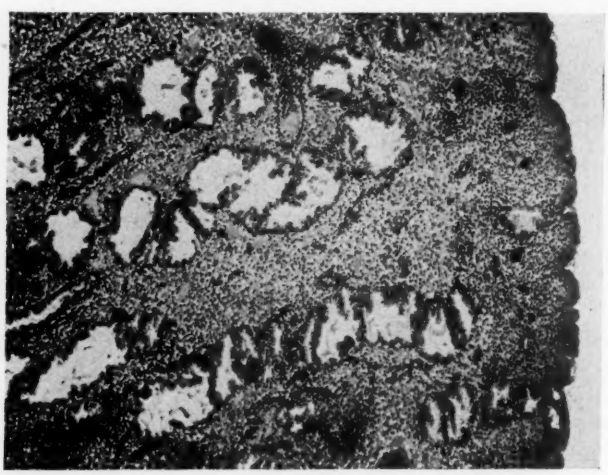

Fig. 3*B*.—Endometrium showing secretory phase, corresponding to twenty-sixth day of the menstrual cycle.

Case 2) of possible artificially induced ovulation is described (Figs. 3*A*, 3*B* and 3*C*):

Case 2.—Table IV. H. H., 42 years of age. Menses began at age of 13, occurred every twenty-eight days and lasted three days. She was admitted because of symptoms caused by multiple uterine fibromyomas. A total of 6,000 R.U. of gonadotropic factor was administered intramuscularly during the seventeenth to

the twentieth day of the cycle, in daily doses of 1,500 R.U.; 17,500 R.U. of A.P.L. were given from the twenty-first to the twenty-fifth day of the cycle, by daily, intramuscular injections of 2,500 R.U. At operation, performed on the twenty-sixth day, the right ovary contained a mature corpus luteum, while the left ovary revealed the presence of a recent stigma, the minute opening containing an adherent blood clot. A supravaginal hysterectomy and bilateral salpingo-oophorectomy were performed.

Gross Pathology of the Ovaries.—The right ovary was normal in size and configuration. A corpus luteum was present which on section appeared to be that of the current menstrual cycle. Several sections through the ovary revealed a few small, 3 to 4 mm., cystic follicles, 2 of which showed slight hemorrhage in their walls. The left ovary was normal in size. Section revealed a cystic follicle measuring 1.25 cm. in diameter, in addition to 4 small follicle cysts, the walls of which had a suggestive bluish tinge. A small punctum containing blood was seen, which when cut was found to be connected with a collapsed follicle with grayish, hemorrhagic walls.

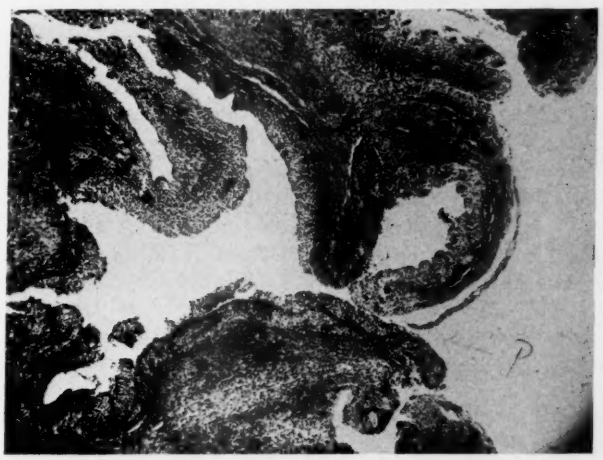

Fig. 3*C*.—Ruptured follicle, resembling recent ovulation. Note serpiginous wall; granulosa cell growth; theca proliferation and luteinization; perifollicular hemorrhage and punctum.

Microscopic Examination.—The corpus luteum structure found in the right ovary presented the characteristics of a normal, mature, active structure which would correspond to that expected on the twenty-sixth day of the cycle (Fig. 3*A*). The uterine endometrium, likewise, showed an advanced secretory phase (Fig. 3*B*). The collapsed, ruptured follicle in the left ovary showed the histologic characteristics found in a recently ruptured Graafian follicle, viz., irregular, serpiginous outline, an inner layer of active follicle cells not yet luteinized, and proliferating theca interna cells with conspicuous luteinization (Fig. 3*C*). In addition, there was marked hemorrhage and congestion about the theca interna and particularly at the point of rupture. The other cystic follicles were atretic follicles with a varying degree of granulosa cell and theca cell stimulation and perifollicular hemorrhage and congestion.

Although the evidence suggests an artificially induced, additional ovulation late in the postovulatory phase, this diagnosis is open to question. The same picture may be produced by rupture of a stimulated, cystic follicle near the ovarian surface by increase in follicle fluid and disruption of the thin segment of ovarian tissue by excessive perifollicular hemorrhage.

The histologic changes following the combination of hypophyseal and chorionic gonadotropins are similar to those seen after the hypophyseal gonadotropin alone, except that all of the 5 cases showed some measure of response. In 2 of the 5 cases, the intensity of reaction was marked. This, however, could not be attributed to a synergistic action, since equally pronounced effects were encountered in which an equivalent or smaller amount of hypophyseal gonadotropin was used. Mazer and Ravetz[23] recently reported profound changes in the human ovary with the use of synapoidin (Parke, Davis & Co.), a combination of chorionic gonadotropin and a pituitary extract containing very little of the gonadotropic substance. In 16 patients the authors found "multiple hemorrhagic follicles with luteinized granulosa layers in all but one, multiple small and large aberrant corpora lutea, hemorrhage into the stroma and intense edema." In our cases, such synergistic activation was not evident.

Hypophyseal and Equine Combination.—A combination of hypophyseal and equine gonadotropins was used in 9 patients, 36 to 46 years of age. These were given concurrently or one before the other, over periods of several days. The dosage of anteron varied from 800 to 16,000 units, and the gonadotropic factor from 6,000 to 15,000 R.U. In one of the 9 cases, the gross and histologic evidence suggested the possibility of a single induced ovulation (Case 1, Table V). The microscopic features in this instance were similar to those produced by the hypophyseal and chorionic gonadotropin. The combined use of hypophyseal and equine gonadotropins resulted in histologic changes which did not differ noticeably from those following the administration of the hypophyseal factor alone. Augmentation of the stimulating effects was not observed.

Combination of Equine and Chorionic Gonadotropins.—In 10 cases, a combination of equine and chorionic gonadotropes was employed. The total dosage of A.P.L. varied from 5,000 to 25,000 R.U.; of gonadogen, from 90 to 350 units; of anteron, from 10,800 to 12,000 units; and of gonadin, from 1,000 to 5,400 units. Artificial ovulation did not result (Table II). The histologic changes were definitely less marked than following any of the combinations which included the hypophyseal factor.

Combination of Chorionic Gonadotropin and Stilbestrol.—(Table VII) Williams[24] has reported an augmentation of the gonadotropic effect of pregnant mares' serum in animals simultaneously receiving stilbestrol. Pencharz[25] showed a similar synergistic action in animals with chorionic gonadotropin and certain estrogens. Simpson, Evans, Fraenkel-Courat and Hao Li[26] combined stilbestrol with chorionic gonadotropin in hypophysectomized rats.

To ascertain if this effect was applicable to the human female, 6 cases, varying from 37 to 50 years of age, were given chorionic gonadotropin and stilbestrol (Table VII). Histologic examination of the ovaries failed to reveal evidence of induced ovulation or of any synergistic action. The perifollicular hemorrhage or congestion was no greater than has been encountered in cases treated with chorionic gonadotropin alone.

TABLE V. EFFECTS OF A COMBINATION OF HYPOPHYSEAL AND EQUINE SERUM GONADOTROPINS UPON OVULATION IN THE HUMAN BEING

NO.	AGE	MENSTRUAL INTERVAL	HYPOPHYSEAL AND EQUINE SERUM GONADOTROPINS	NO. OF UNITS	ROUTE†	INJECTION DAY OF CYCLE	OPERATION DAY OF CYCLE	ENDOMETRIUM	CURRENT C.L. OR EARLY CURRENT RUPTURED FOLLICLE (C.R.F.)	INDUCED OVULATION
1	40	28	Gonad. Factor* Gonadin	6,000 R.U. 3,000	IM IM	19-22 19-23	24	Secretory	+	+
2	45	28	Gonad. Factor* Gonadin	10,500 R.U. 3,000	IM IM	Gravid		Decidua	+	0
3	44	Menomet.	Gonad. Factor* Anteron	6,000 R.U. 1,200 I. U.	IM IV	--	+1	Proliferative	0	0
4	38	25-30	Gonad. Factor* Anteron	6,000 R.U. 1,200 I.U.	IM IV	30, 1-3 3-5	6	Proliferative	0	0
5	46	26-40	Gonad. Factor* Anteron	15,000 R.U. 14,000	IM IV	17-24 18-24	25	Proliferative	0	0
6	44	29	Gonad. Factor* Anteron	12,000 R.U. 16,000	IM IV	13-20	21	Proliferative	0	0
7	44	28-30	Gonad. Factor* Anteron	12,000 R.U. 10,000	IM IV	28, 1-7 3-7	8	Proliferative	0	0
8	36	28	Gonad. Factor* Anteron	6,000 R.U. 800	IM IV	13-15 11-12	16	Secretory	+	0
9	38	30	Gonad. Factor* Anteron	12,500 R.U. 10,000	IM IV	19-23	24	Proliferative	0	0

*Collip.
†IM, Intramuscular; IV, intravenously.

TABLE VI. EFFECTS OF A COMBINATION OF EQUINE SERUM AND CHORIONIC GONADOTROPINS UPON OVULATION IN THE HUMAN BEING

NO.	AGE	MENSTRUAL INTERVAL	EQUINE SERUM AND CHORIONIC GONADOTROPINS	NO. OF UNITS	ROUTE	INJECTION DAY OF CYCLE	OPERATION DAY OF CYCLE	ENDOMETRIUM	CURRENT C.L. OR EARLY CURRENT RUPTURED FOLLICLE (C.R.F.)	INDUCED OVULATION
1	48	28	Gonadogen* A.P.L.	200 U. 5,000 R.U.	IV IM	35-38 39-41	50	Proliferative	0	0
2	49	28	Gonadogen* A.P.L.	180 U. 10,000 R.U.	IV IM	26-29 30-32	33	Secretory	+ (double)	0
3	47	28	Gonadogen* A.P.L.	170 U. 10,000 R.U.	IV IM	24-27 28-30	33	Proliferative	0	0
4	36	28	Gonadogen* A.P.L.	350 U. 7,500 R.U.	IV IM	24-30 28-30	31	Late Prolif.	+	0
5	47	28	Gonadogen* A.P.L.	120 U. 7,500 R.U.	IV IM	30 32-34	35	Proliferative	0	0
6	47	Postmenop.	Gonadogen* A.P.L.	90 U. 15,000 R.U.	IV IM	Postmenopausal		Hypoplasia	0	0
7	34	28	Anteron A.P.L.	10,800 I.U. 22,500 R.U.	IV IM	16-23	24	Secretory	+	0
8	31	28	Anteron A.P.L.	12,000 I.U. 25,000 R.U.	IV IM	27 and 1-9	10	Early Secretory	C.R.F.-(double)	0
9	30	28	Gonadin A.P.L.	5,400 U. 12,500 R.U.		37-41 42-44, 1-2	3	Proliferative	0	0
10	30	28	Gonadogen* Gonadin† A.P.L.	100 1,000 17,500 R.U.	IV IM IM	5-7 6 8-11	12	Secretory	+	0

*Cartland-Nelson unit.
†Cole-Saunders unit.

TABLE VII. EFFECTS OF A COMBINATION OF CHORIONIC GONADOTROPINS AND ESTROGENS UPON OVULATION IN THE HUMAN BEING

NO.	AGE	MENSTRUAL INTERVAL	CHORIONIC GONADOTROPIN AND STILBESTROL	DOSAGE	ROUTE*	INJECTION DAY OF CYCLE	OPERATION DAY OF CYCLE	ENDOMETRIUM	CURRENT C.L. OR EARLY CURRENT RUPTURED FOLLICLE (C.R.F.)	INDUCED OVULATION
1	45	28	A.P.L. Stilbestrol	25,000 R.U. 25 mg.	IM PO	31-35	36	Secretory	+	0
2	37	27	A.P.L. Stilbestrol	25,000 R.U. 25 mg.	IM PO	13-17	18	Secretory	+	0
3	45	21	Stilbestrol Pranturon	15 mg. 4,500 I.U.	PO IM	10-13 12-13	14	Early Secr.	+	0
4	50	28	Stilbestrol Pranturon	22 mg. 3,750 I.U.	PO IM	20-23 21-23	24	Secretory	+	0
5	38	28-30	Stilbestrol Pranturon	36 mg. 11,250 I.U.	PO IM	22-29 25-29	30	Adv. Prolif.	0	0
6	40	30	Stilbestrol Pranturon	31 mg. 9,000 I.U.	PO IM	18-24 21-24	25	Secretory	+	0

*IM, Intramuscularly; per os.

SUMMARY

The effect of a variety of gonadotropins upon the human ovary was studied in a series of 91 cases.

The following gonadotropins were used: hypophyseal, chorionic, pregnant mares' serum; combination of chorionic and hypophyseal, chorionic and equine, and chorionic and stilbestrol.

The histologic alterations in the human ovary caused by the various gonadotropins differed quantitatively rather than qualitatively. The intensity of reaction was most marked following the hypophyseal gonadotropins, decidedly less with equine, and least with the chorionic gonadotropins. The histopathologic ovarian changes in the majority of instances in which the hypophyseal gonadotropin was administered, included enlargement of cystic follicles, proliferation of the granulosa cells lining these follicles, proliferation and luteinization of the theca interna cells, perifollicular congestion and hemorrhage, and occasional edema and congestion of the ovarian parenchyma. With the equine gonadotropin, similar alterations were noted, but in a smaller percentage of cases and to a lesser degree. The only conspicuous effect of the chorionic gonadotropin was the production of perifollicular congestion and hemorrhage.

No synergistic effects were observed with any of the gonadotropin combinations. The response to the hypophyseal and chorionic or the hypophyseal and equine gonadotropins did not materially differ from those following the use of the pituitary extract alone. The combination of equine and chorionic gonadotropins had no greater effect than that induced by the sum of the individual components. Stilbestrol was not found to enhance the activity of the chorionic hormone.

In no instance was evidence of ovulation found which could be unquestionably attributed to the administered gonadotropins.

The absence of any increase in the number of maturing Graafian follicles, the absence of ova or degenerative remnants of ova in the cystic follicles, and the absence of induced ovulations suggests that, while the available gonadotropins may stimulate those granulosa and theca interna cells, in follicles undergoing atresia, which are still capable of response, they apparently do not induce follicle maturation or stimulate the development of follicles containing normal ova to maturity and ovulation.

For the materials used in this investigation, we are indebted to the following: Schering Corporation, anteron, pranturon; Ayerst, McKenna and Harrison, Ltd., A. P. L., gonadotropic factor, stilbestrol; Cutter Laboratories, gonadin; The Upjohn Company, gonadogen; Eli Lilly and Company, stilbestrol; E. R. Squibb & Sons, antuitrin.

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DISCUSSION

DR. HERBERT F. TRAUT, New York, N. Y.—If I am correct, the authors conclude that none of the gonadotropic substances used, singly or in combination with other substances, produced conclusive evidence of the maturation of Graafian follicles, ovulation, or luteinization of the ruptured follicles. In short, their findings negate the results of other workers in the field and indicate that we are farther than we had hoped from the solution of the physiologic relationships of the anterior hypophysis and that, furthermore, therapeutic attempts with these substances are useless.

In view of these generally negative findings, it may be well for us to examine some of the details of the experiment which may account for this result. At once one is impressed with the age range of the patients who formed the subjects for this experiment. Of the 91 women, 72 were over 35 years of age and 52 were over 40. In other words, over three-fourths of them had entered the last or involutional phase of reproductive life. This in itself would be meaningless were it not for the fact that we know that the Graafian follicle apparatus is normally more refractory at this time and that failure of maturation and ovulation are extremely common. The authors may be said therefore to have commenced with their experiment weighted somewhat in a negative direction. Had greater success in stimulating the follicle been the result, this weighting would have proved an advantage and made the results all the more convincing; on the other hand, the fact that they failed to evoke ovulation except in two possible instances must be taken with some reserve.

It is true that a cellular response was frequently noted which would indicate that some of the gonadotropic substances had produced growth of thecal and granulosal elements which, though not normal in many respects, were interpreted as the result of definite stimulative properties. Here the matter of control enters in very definitely. The authors studied the ovaries of 25 women who were thought to be normal and used this as a basis for judgment of the abnormal. Because of the care the authors used in arriving at their conclusions, I am inclined to accept the evidence and the conclusions reached and to feel that they have arrived at a very correct result.

All available evidence seems to indicate that the hypophysis excretes gonad-stimulating substances at a constant rate. That is, there is no quantitative cyclical variation. Therefore, why should one suppose that increased amounts introduced by any means would result in increased activity of the ovary? The cyclical variation in the follicular apparatus of the ovary is in all probability not due to variations in gonadotropic stimulators but to variations in some synergistic substance which makes the gonad susceptible, periodically, to the secretions of the anterior lobe. The most likely substance which could have this effect is thyroxin and, as Gunbrecht and Loesser have shown, is in all probability essential to the periodic response of the ovarian elements. I am therefore very sorry that the present authors did not include thyroxin in their list of substances to be tested in combination with the gonadotropes.

This study represents the most complete and thorough study of the effect of gonadotropic substances on the human ovary which has thus far appeared. I feel

that although the findings are negative and we can accept them only with reserve, the work is a tremendous step forward, and this study should form the basis for further studies which will be more fruitful, particularly if younger subjects and perhaps other synergistic substances can be employed with the gonadotropic substances.

DR. EMIL NOVAK, BALTIMORE, MD.—There is much need of just such papers as this. The problem is not an easy one to approach experimentally in the human female, because of the difficulty of proper scientific control. Anyone familiar with the structure of the ovary knows the enormous variation in the histology of individual ovaries, even within the limits of normality. While Dr. Geist made genuine efforts to control his studies, there are few of the pictures which he has shown in ovaries which had been treated by gonadotropes which are not encountered in the routine laboratory study of ostensibly normal ovaries.

The objections which are urged by Dr. Traut are valid, although I do not believe they are of decisive importance in evaluating the results of this study. What we are hoping for with gonadotropic preparations is an effect as striking as that seen, for example, in the ovaries of certain experimental animals, an effect so clear-cut as to leave nothing to the imagination, such as pronounced follicle-ripening, luteinization, and ovulation. Such effects Dr. Geist, in common with a number of excellent investigators, and in contrast with one or two authors whose results have been much publicized by manufacturers, has been unable to obtain.

Mention has been made of the remarkable ovarian reaction seen in some cases of hydatidiform mole and chorionepithelioma. The pertinence of this to the present problem has seemed to me to have been insufficiently stressed. When we can explain this reaction satisfactorily we will have advanced a long way in our knowledge of the mechanism of gonadotropic activity in the human ovary.

The extreme ovarian response in hydatidiform mole and chorionepithelioma is at least the indirect result of an exaggerated chorionic gonadotrope production, and yet such studies as Dr. Geist has reported indicate that this same hormone has little effect upon ovarian histology. How can this seeming paradox be explained? The natural suggestion would seem to be that the ovarian reaction in these abnormal pregnancy conditions is due to the pituitary rather than the chorionic gonadotropic principles, and that the latter serve in some way to motivate or activate the former. The problem is still unsolved, in spite of much experimental study, such as that of Evans and his associates.

Finally, such papers as this should serve a valuable purpose in curbing the present therapeutic abuse of so-called gonadotropic commercial preparations. I know of none which have been more widely misused in the past two years than the hormone preparations of pregnant mare's serum. All over the country today sterile women are receiving "shots" of this substance, usually on the basis of very inadequate study, often in the absence of any endocrine dysfunction whatsoever, and almost always with no benefit. There can be no objection to a discriminating employment of the equine gonadotrope, experimental though it still is, but we should take a firm stand against the slipshod use of this and other gonadotropes which are now so widely prevalent.

DR. J. HOFBAUER, CINCINNATI, OHIO (by invitation).—I believe that the utilization of gonadotropins at present available, should be discarded. They have not proved of value in stimulating ovarian function. Our observation of the formation of multiple cysts in the ovary following its use may serve as a warning.

A specific gonadotropin factor is available, however, by the application of low dosage x-ray to the pituitary as recommended by me in 1922 and 1923. Observations of recurrence of menstruation and ovulation, and occasionally pregnancy, combine to recommend this method, if used with caution and discernment.

DR. GEIST (closing).—I am in accord with Dr. Traut on most of the points. As far as the age of the patient is concerned, the patients of 25 showed no variation from those of more advanced age. I do not believe one can accuse a woman of 35 of possessing "refractory ovaries."

Dr. Novak, I believe, sensed the real significance of the paper. It had two aspects, one a scientific and the other a very practical one. The practical one was to disseminate the idea that all the things one reads in the literature may not be true. A good deal has been written recently about the gonadotropins and much damage has been done, as Dr. Novak emphasized, perhaps not to the patient's well-being but certainly to her pocketbook.

As far as radiation of the pituitary is concerned, I have had no experience with it in human beings in relation to stimulating ovarian function. It might be a very fruitful field for investigation. It is certainly not harmful, and we have used it in the menopause without any untoward results.

TIME OF ONSET AND DURATION OF THE TOXEMIAS OF LATE PREGNANCY IN RELATION TO THE DEVELOPMENT OF PERMANENT VASCULAR DAMAGE*

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THE post-partum follow-up of patients who have recently suffered from one of the toxemias of late pregnancy is a relatively new addition to the practice of obstetrics. Formerly it was considered that necessary care ended some fourteen days after delivery. Later, certain individual physicians and clinics requested their patients to return six weeks post partum, but examination at this time was aimed at the detection of pelvic abnormalities resulting from labor rather than the after-effects of the toxemias. In 1924 Harris published a statistical study on a number of toxemic patients examined one year after delivery and found that certain of them evidenced an apparently persistent hypertension at that time. Since then a relatively voluminous literature has been accumulated indicating the frequency with which essential hypertension, chronic nephritis, or as it is now better known, chronic vascular disease follows toxemic pregnancy. Although we have become aware of the frequency with which chronic damage is to be found subsequent to a toxemic episode, many pertinent questions remain unanswered. For example, it is often impossible to state whether the vascular condition antedated the pregnancy or resulted from the toxemia. Indeed it has been suggested that the former is universally the case, but that the abnormal condition of the arterioles had been too slight to be detected previously by any known means of examination. Furthermore, quite frequently, the differential diagnosis between chronic vascular disease and so-called "toxemia of pregnancy" cannot be made during gestation but must await prolonged follow-up study. It has been suggested that the only real aids toward immediate diagnosis are the parity of the patient (chronic vascular damage being observed most frequently in multiparas), careful examination of the eye grounds, and the month of onset of toxemic manifestations.

It has for some time been my opinion that the time element is of importance with regard to the toxemias in two ways: in the first place, in relation to the month of gestation when signs and symptoms appear and, in the second place, in relation to the number of weeks elapsing between their appearance and the termination of pregnancy. In an effort to clarify this dual problem a study has been made of 500 patients observed at the Johns Hopkins Hospital throughout a pregnancy complicated by toxemia, and subsequently followed at intervals of three months for from two to twelve years after delivery. All of these

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women were apparently normal when first seen in the prenatal clinic, and for inclusion in this series it was required that a minimum of three dispensary visits be made, during which time the blood pressure was normal, the urine free from albumin, and other signs and symptoms of toxemia absent. A moderate number had evidenced some form of toxemia in a previous pregnancy but apparently had returned entirely to normal during their routine post-partum follow-up.

The 500 cases comprising this study were first separated into several groups according to the lunar month of pregnancy when toxemic manifestations first appeared. Subsequent analyses of these groups follow:

Time of Onset of Toxemia and Race of Patients.—Table I indicates the makeup of the series of patients according to the month of onset of toxemia. It will be noted that the numbers decrease as the earlier months of pregnancy are reached. This is due to the fact that relatively few clinic patients reported early enough to satisfy the previously mentioned criterion of three normal dispensary examinations. Although the total number of patients delivered in the hospital was about equally divided as to race, the colored considerably outnumbered the white in this series. This difference has been found to exist whenever studies on the toxemias have been made and apparently represents a true racial effect.

TABLE I. GENERAL MAKE UP OF SERIES OF TOXEMIC PATIENTS STUDIED. MONTH OF ONSET OF TOXEMIA DIVIDED ACCORDING TO RACE OF PATIENT

RACE	TERM	9 MO.	8 MO.	7 MO.	6 MO.	5 MO.	4 MO.	TOTAL
White	29	69	32	36	18	16	12	212
Black	46	74	59	47	23	16	23	288
Total	75	143	91	83	41	32	35	500

Parity of Patients.—It will be noted from Table II that the number of multiparas in the series was approximately the same as that of primigravidas, the percentage being 53.60 per cent and 46.40, respectively. This table shows very clearly that in primigravidas the tendency for a toxemia to develop increases month by month until term, while conversely in multiparas the opposite is true; indeed, some 85 per cent of the toxemias developing at the fourth or fifth month are in multiparas while in this group the development of this complication late in pregnancy is much less common. Confirmation of this statement appears in the table under "Mean parity" and shows a parous mean of 1.92 in the term group with a steady rise to 4.71 when signs and symptoms appeared as early as the fourth month.

Blood Pressure and Albuminuria at Discharge.—In order to demonstrate statistically the incidence of patients whose blood pressure was within normal limits or abnormally high at the time of discharge from the hospital, an arbitrary yardstick of 140 mm. systolic and 90 mm. diastolic was chosen as the level of beginning hypertension. Table III shows a fairly steady increase in systolic hypertension at discharge as the time of onset of the toxemia recedes from term to the earlier months of pregnancy. Thus, when the toxemia manifested itself first at the end of gestation only one patient in twenty left the hospital with a systolic pressure of 140 or above, whereas in the group whose first signs and symptoms began during the fourth month a similarly adduced ratio of two out of five was found to exist. The trend of diastolic

TABLE II. PARITY OF PATIENTS IN SERIES ACCORDING TO MONTH OF ONSET OF TOXEMIA

PREVIOUS PREGNANCIES	TERM	9 MO.	8 MO.	7 MO.	6 MO.	5 MO.	4 MO.	TOTAL
0	55	85	39	31	12	5	5	232
1 or more	20	58	52	52	29	27	30	268
i	5	20	8	9	9	6	2	59
ii	8	11	11	12	4	5	5	56
iii	1	11	8	10	5	5	9	49
iv	1	6	5	5	3	1	4	25
v	2	5	2	2	2	3	2	18
vi		2	3	6		2	1	14
vii		1	3	1			3	8
viii	1		7	1	3	1		13
ix			2	2		2	2	8
x	1	1	2		2	1	2	9
xi				1	1	1		3
xii			1	2				3
xiii	1	1						2
xiv				1				1
Primiparas Per cent	73.33	59.44	42.86	37.35	29.27	15.62	14.29	46.40
Multiparas Per cent	26.67	40.56	57.14	62.65	70.73	84.38	85.71	53.60
Mean parity including present pregnancy	1.92	2.16	3.52	3.54	3.66	4.41	4.71	3.05

TABLE III. BLOOD PRESSURE AND ALBUMINURIA AT TIME OF DISCHARGE ACCORDING TO MONTH OF ONSET OF TOXEMIA

	PER CENT OF TOTAL						
	TERM	9 MO.	8 MO.	7 MO.	6 MO.	5 MO.	4 MO.
Systolic Pressure							
To 139	94.67	83.81	79.55	76.25	64.11	77.42	60.00
140 and over	5.33	16.19	20.45	23.75	35.89	22.58	40.00
Diastolic Pressure							
To 89	76.00	69.72	54.54	66.25	46.15	70.97	48.57
90 and over	24.00	30.28	45.46	33.75	53.85	29.03	51.43
Albuminuria							
0	84.00	71.13	76.40	65.00	71.79	90.32	80.00
Trace or +	16.00	28.87	23.60	35.00	28.21	9.68	20.00

change from month to month is like that of systolic pressure. It should be noted, however, that for each monthly bracket the percentage of patients with an abnormally high diastolic pressure is greater than that recorded for systolic. The incidence of albuminuria at the time of discharge varied markedly from month to month, but there was no steady change. We have felt for some time that the presence or absence of albumin in the urine is without value as a criterion for the immediate or remote prognosis of a case of toxemia of pregnancy.

Blood Pressure and Albuminuria Six Weeks Post Partum.—Table IV has been constructed on the same basis as its predecessor and shows the incidence of hypertension and albuminuria six weeks post partum. Although the incidence of abnormally high blood pressure readings, both systolic and diastolic, is considerably greater at this time than at discharge from the hospital, the same trend of increase is noted as the onset of toxemia extends back into the earlier months of pregnancy.

TABLE IV. BLOOD PRESSURE AND ALBUMINURIA SIX WEEKS POST PARTUM ACCORDING TO MONTH OF ONSET OF TOXEMIA

	PER CENT OF TOTAL						
	TERM	9 MO.	8 MO.	7 MO.	6 MO.	5 MO.	4 MO.
Systolic Pressure							
To 139	60.42	53.26	28.30	41.17	24.00	35.00	15.00
140 and over	39.58	46.74	71.70	58.83	76.00	65.00	85.00
Diastolic Pressure							
To 89	40.42	53.27	28.30	25.49	24.00	35.00	15.00
90 and over	59.58	46.73	71.70	74.51	76.00	65.00	85.00
Albuminuria							
0	89.54	92.39	90.57	92.16	92.00	95.00	95.00
Trace or +	10.46	7.61	9.43	7.84	8.00	5.00	5.00

Probably the most important item to be noted in this chart is that even six weeks after delivery many patients ultimately found to be normal still evidenced hypertension. Conversely, normal readings were frequently obtained on individuals who later were diagnosed as having chronic vascular disease. The presence of albumin in the urine did not show the above trend, and positive results were obtained more frequently in the higher as contrasted with the lower monthly brackets. Throughout, albuminuria was noted less frequently at the examination six weeks after delivery than at the time of discharge from the hospital.

TABLE V. BLOOD PRESSURE AND ALBUMINURIA TWO TO TEN YEARS AFTER DELIVERY ACCORDING TO MONTH OF ONSET OF TOXEMIA

	PER CENT OF TOTAL						
	TERM	9 MO.	8 MO.	7 MO.	6 MO.	5 MO.	4 MO.
Systolic Pressure							
To 139	81.33	65.03	32.93	21.68	7.32	0.00	5.71
140 and over	8.67	34.97	67.07	78.32	92.68	100.00	94.29
Diastolic Pressure							
To 89	77.33	66.43	34.07	22.89	12.20	3.13	5.71
90 and over	22.67	33.57	65.93	77.11	87.80	96.87	94.29
Albuminuria							
0	93.33	93.00	85.71	81.93	95.12	90.62	91.43
Trace or +	6.67	7.00	14.29	18.07	4.88	9.38	8.57

Blood Pressure and Albuminuria Two to Ten Years After Delivery.—Table V shows the results of examination of the 500 patients two to ten years after delivery. The readings used to make up this chart were the last obtained in the toxemia clinic prior to the time the data for this paper were accumulated (November, 1940). They indicate well the high incidence of chronic hypertension found in a group of patients who, prior to a toxemic pregnancy, were apparently normal in this regard. Furthermore the marked increase in incidence of hypertension as the toxemia manifested itself earlier and earlier in pregnancy, should be noted. Thus when signs and symptoms were found only at term, or during the ninth and eighth month of pregnancy, 40 per cent of the patients were ultimately found to have both systolic and diastolic hypertension, whereas if the onset was during an earlier month 88 per cent were abnormal in this regard. The incidence of albuminuria again varied markedly in the various monthly brackets but no definite trend was found.

TABLE VI. TOXEMIAS IN PREVIOUS PREGNANCIES IN MULTIPARAS OF SERIES ACCORDING TO MONTH OF ONSET OF TOXEMIA IN PRESENT PREGNANCY

	TERM	9 MO.	8 MO.	7 MO.	6 MO.	5 MO.	4 MO.	TOTAL
Total multiparas	20	58	52	52	29	27	30	268
Eclampsia in previous pregnancy	1	1	0	0	3	3	4	12
Other toxemia in previous pregnancy	9	18	23	27	15	15	14	121
Total toxemia in previous pregnancy	10	19	23	27	18	18	18	133
Per cent toxemia in previous pregnancy	50.00	32.76	44.23	51.92	62.07	66.67	60.00	49.62

Toxemia in Previous Pregnancies.—Table VI shows that of the total 268 multiparas in the series, 131 or approximately one-half of them had evidenced a toxemia in a previous pregnancy. The incidence of previous toxemia was somewhat less in patients who developed late toxemia (eight months to term) than in those who developed it at an early date (four to seven months).

Toxemia in Subsequent Pregnancies.—Of the 500 cases studied in the series, 207 of them were observed in one or more subsequent pregnancies. Of these, 147, or 71.01 per cent, again evinced toxemia, as is shown in Table VII. The incidence of repeated toxemia was lowest in the

TABLE VII. INCIDENCE OF TOXEMIA IN SUBSEQUENT PREGNANCIES ACCORDING TO MONTH OF ONSET OF TOXEMIA IN PRESENT PREGNANCY

	TERM	9 MO.	8 MO.	7 MO.	6 MO.	5 MO.	4 MO.	TOTAL
Total patients with subsequent pregnancies	32	63	38	26	19	14	15	207
Total patients with toxemia	9	35	33	23	18	14	15	147
Per cent of patients with toxemia	28.12	55.55	86.84	88.46	94.74	100.00	100.00	71.01

"term" group and rose rapidly. Of those patients whose analyzed toxemia began at the eighth month or less, only 9, or 8 per cent, were observed with a subsequent normal pregnancy.

Incidence of Chronic Vascular Damage According to Month of Onset of Toxemia.—Following these statistical summaries of pertinent data accumulated from the 500 cases of toxemia of pregnancy under discussion, we now reach the most significant part of the discussion, namely the end result in terms of chronic vascular damage. In this latter category are included all patients evidencing vascular and renal disease. The vast majority of them were found to have cardiovascular renal disease, a few chronic hemorrhagic nephritis, and there was one instance of apparent nephrosis. As has been said, all of the patients were apparently normal at the onset of the toxemic pregnancy; yet according to Table VIII, 63.40 per cent were ultimately found to show chronic damage. The incidence of this was two and three-quarters times as high in the multiparous as in the primiparous portion of the group. Obviously the future prognosis for the multipara with toxemia is extremely bad, and *when the condition first evidenced itself at the seventh lunar month or earlier no multipara was found on late return to be normal.* The prognosis for the primipara is generally less discouraging unless the first manifestations occur before the last trimester

of pregnancy, in which case, according to our analysis, chronic vascular damage is relatively certain to follow.

TABLE VIII. INCIDENCE OF CHRONIC VASCULAR DAMAGE ACCORDING TO MONTH OF ONSET OF TOXEMIA

MONTH OF ONSET	PRIMIPARAS			MULTIPARAS			TOTAL PATIENTS		
	TOTAL PATIENTS	CHRONIC VASCULAR DAMAGE	PER CENT	TOTAL PATIENTS	CHRONIC VASCULAR DAMAGE	PER CENT	TOTAL PATIENTS	CHRONIC VASCULAR DAMAGE	PER CENT
Term	55	5	9.09	20	15	75.00	75	20	26.67
9 mo.	85	19	22.35	58	40	68.97	143	59	41.26
8 mo.	39	15	38.46	52	48	92.31	91	63	69.23
7 mo.	31	16	51.61	52	52	100.00	83	68	81.93
6 mo.	12	11	91.67	29	29	100.00	41	40	97.56
5 mo.	5	5	100.00	27	27	100.00	32	32	100.00
4 mo.	5	5	100.00	30	30	100.00	35	35	100.00
Total	232	76	32.76	268	241	89.93	500	317	63.40

TABLE IX. INCIDENCE OF CHRONIC VASCULAR DAMAGE ACCORDING TO TIME ELAPSING BETWEEN ONSET OF TOXEMIA AND DELIVERY

WEEKS OF TOXEMIA	PRIMIPARAS			MULTIPARAS			TOTAL PATIENTS		
	TOTAL PATIENTS	CHRONIC VASCULAR DAMAGE	PER CENT	TOTAL PATIENTS	CHRONIC VASCULAR DAMAGE	PER CENT	TOTAL PATIENTS	CHRONIC VASCULAR DAMAGE	PER CENT
1-2	115	19	16.52	55	36	65.45	170	55	32.35
3-4	47	9	19.15	35	28	80.00	82	37	45.12
5-6	18	7	38.89	26	25	96.15	44	32	72.73
7-8	11	7	63.64	30	30	100.00	41	37	90.24
9-12	24	17	70.83	39	39	100.00	63	56	88.89
13-16	8	8	100.00	29	29	100.00	37	37	100.00
17-20	4	4	100.00	28	28	100.00	32	32	100.00
21 and over	5	5	100.00	26	26	100.00	31	31	100.00
Total	232	76	32.76	268	241	89.93	500	317	63.40

Incidence of Chronic Vascular Damage According to Weeks Elapsing Between Onset and Delivery.—Table IX indicates the late outcome to the patients in the series according to the number of weeks elapsing between the first appearance of signs and symptoms of toxemia and termination of the pregnancy. Although a few instances of apparent postmaturity were noted, in an appreciable number the delivery was premature. This latter group was sometimes spontaneous, but was more often the result of artificial induction of labor or cesarean section. The table shows that in no instance was a primipara with toxemia carried for more than twelve weeks (three lunar months) without chronic damage resulting, while six weeks (one and one-half lunar months) was a similar dividing line in the multiparous group.

It is our opinion that the number of weeks elapsing between the onset of toxemia and delivery is of greater importance in determining the final outcome than the month of onset. As an example, the author has observed a patient who, as a primigravida, developed at the fifth month a toxemia sufficiently severe to require immediate termination of the pregnancy. A year later, after thorough medical study, she was found to be completely free of signs or symptoms of chronic vascular disease.

From the standpoint of the future, it is unfortunate that so many of the toxemias occurring early in pregnancy run an apparently benign course, and hence gestation is allowed to continue. It is our feeling that the later interests of the patient would often be better served if after a maximum of four weeks' observation the pregnancy were terminated, for it seems entirely possible that such a plan would allow most patients to return completely to normal, when, at a later date, another pregnancy might possibly eventuate without complication.

TABLE X. OUTCOME IN SUBSEQUENT PREGNANCIES ACCORDING TO TIME ELAPSING BETWEEN ONSET OF TOXEMIA AND DELIVERY

WEEKS OF TOXEMIA	TOTAL PATIENTS	TOXEMIA	PER CENT TOXEMIA
1-2	72	32	44.44
3-4	30	16	55.33
5-8	35	31	88.57
9-12	24	22	91.67
13 and over	46	46	100.00
Total	207	147	71.01

Outcome in Subsequent Pregnancies According to Weeks Elapsing Between Onset and Delivery.—Table X indicates the outcome to be expected in a subsequent pregnancy according to the number of weeks elapsing between the onset of toxemia and delivery in the pregnancy under study. As has been said, the prognosis is generally bad. However, there appears again a sharp difference in results if the pregnancy is carried on for less than four weeks or for more. In the first group the incidence of chronic vascular damage was 47 per cent as contrasted with 94 per cent in the latter.

Repeated Toxemia.—Although possibly not a pertinent part of this study, the following pieces of information were obtained on the remote effects of repeated toxemia and seem worthy of note here:

1. Two hundred and twenty-seven patients were observed who had a toxemia either in a previous *or* a subsequent pregnancy in addition to the toxemia included in this study. Of these only four, or 1.76 per cent, were apparently normal when last seen.

2. One hundred and thirty-three patients were observed who had had a toxemia in a *previous* pregnancy. Of these, only three, or 2.26 per cent, were apparently normal when last seen.

3. One hundred and forty-seven patients were observed who had a toxemia in a *subsequent* pregnancy. Of these, one, or 0.68 per cent, was apparently normal when last seen.

4. Fifty-three patients were observed who had a toxemia *both* in a previous and a subsequent pregnancy. Of these none remained normal.

SUMMARY AND CONCLUSIONS

A statistical analysis has been presented of 500 patients who were followed through pregnancies complicated by toxemia. Although some of these patients had had toxemia in a previous pregnancy, all were apparently normal when first seen during the present one.

The cases were first divided according to the lunar month of onset of toxemic signs and symptoms. It was found that the race and age of the patient, the degree of hypertension and amount of albuminuria during pregnancy, the type of delivery and the result to the child, all

failed to show significant changes according to the month of onset. The incidence of multiparas in the various groups increased as the time of onset fell back into the earlier months of gestation. If the toxemic condition became manifest near the beginning of gestation, the number of abnormally high blood pressure readings increased, both at the time of the patient's discharge from the hospital and at the six weeks postpartum visit. Even six weeks after delivery many patients ultimately presenting signs of chronic vascular disease had normal blood pressure readings and the converse was also true. In those patients evidencing toxemia early in pregnancy the incidence of previous toxemia was higher than in the group first manifesting abnormality in the later months. A similar trend was noted when an analysis was made according to the outcome of subsequent pregnancies. The incidence of chronic vascular damage was high (63.40 per cent) and was greater among multiparas (89.93 per cent) than primiparas (32.76 per cent). No primipara was seen whose toxemia occurred prior to the sixth month and who remained normal. For the multiparous group the same was true prior to the eighth month.

The series was also divided according to the number of weeks elapsing between the onset of the toxemia and delivery. Here no primipara remained normal who had been carried for more than twelve weeks subsequent to the development of toxemic manifestations. A similar limit of six weeks was found for multiparas. It seems evident that the duration of a toxemia from its beginning to delivery is of more importance from the standpoint of subsequent vascular disease than is the month of onset. Finally, it is believed that termination of the pregnancy in an effort to avoid chronic damage is justified if signs and symptoms persist after four weeks of observation and treatment.

INTERPRETATION OF BLOOD PRESSURE BEHAVIOR DURING PREGNANCY AND THE PUERPERIUM*

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THE discovery that hypertension complicates pregnancy, either early or late in gestation, is rightfully regarded as of serious significance. Since it may indicate either vascular disease or true toxemia, differentiation of these conditions assumes much importance, not only in the management of the pregnancy, but in the final classification and ultimate prognosis of the disorder.

It is our purpose to point out certain observations during pregnancy and the puerperium, which not only aid in interpreting the behavior of the blood pressure, but which enable one to predict that a moderate rise in blood pressure will probably occur in the latter part of pregnancy. It is desired to emphasize, particularly, the value of retinal examination in the differentiation and management of true toxemia and vascular disease, and the importance of examination of the formalin-fixed placenta in the final classification of the disorder.

Assuming the patient presents herself in the first trimester of pregnancy, one may anticipate, even at this early period, a greater likelihood of hypertension of a truly toxic nature, late in pregnancy, if the patient is an adolescent. This fact was noted by us in a previous study[1] and has, no doubt, impressed itself on many observers in the past.

Likewise, if the patient presents certain stigmas of glandular disease, as noted by Vorzeimer and associates,[2] such as disturbance in height-weight ratio, hypothyroidism, pituitary disorder, etc., she is more likely to develop true toxemia of pregnancy.

We have learned to attach great importance to a retinal examination. Early in pregnancy, the arteries are studied particularly for evidence of sclerosis as shown by disturbance in arteriovenous (A-V) ratio, increase in light reflex and occurrence of A-V compressions; late in pregnancy, for evidence of toxemia, as shown by the occurrence of spasms or hemorrhages. In severe toxemia or advanced cardiovascular-renal disease, hemorrhages and whitish exudates may be seen.

The normal relation of the caliber of the artery to that of the vein is 2 to 3, indicating the diameter of the arteries should be two-thirds that of the veins. Arteries of this caliber, being free of sclerosis, do not reflect light and do not compress the vein where the artery may cross it, or cause dilatation of the vein, distal to the point of compression.

For thorough examination of the retina the room should be darkened and the pupils dilated by a mydriatic, such as one drop of 1 per cent homatropine, instilled into each eye, which produces ample dilatation within thirty minutes. Following the examination, the pupils may be quickly constricted to normal size by the use of a miotic, as one drop of

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one-fourth per cent eserine instilled into each eye. No increase of intraocular tension has been noted from the use of these drugs over a period of several years.

We have considered 80 mm. of mercury the upper limit of normal diastolic blood pressure during pregnancy and the puerperium and considered any rise above this figure indicative of hypertension. While there is usually a corresponding rise in systolic blood pressure, the latter is subject to more variations and influences and is not so dependable as an index of hypertension. It is rather a measure of the cardiac effort to sustain adequate circulation in the face of increased peripheral resistance. Considering the fact that the majority of diastolic blood pressures is in the range of 60 to 70 mm. of mercury throughout pregnancy (86 per cent in this series), any rise above 80 mm. of mercury is a danger signal, necessitating observation at five- to seven-day intervals to avoid overlooking a rapidly progressing true toxemia.

If, early in pregnancy, one finds a normal A-V ratio of 2 to 3, the blood pressure is almost invariably normal. If hypertension develops late in pregnancy in these cases, it is almost certain to be on the basis of true toxemia of pregnancy, as substantiated by finding toxic types of infarcts in the placenta or sharp spasms in the retinal arteries. In a few instances, however, we have noted the development of a comparable degree of mild hypertension late in pregnancy, apparently on the basis of vascular disease, with a change, during pregnancy, from a normal A-V ratio of 2 to 3 to one between 1 to 2 and 2 to 3. That such a change may occasionally take place during pregnancy, is supported by the fact that A-V ratios between 1 to 2 and 2 to 3 early in pregnancy, occasionally change to 1 to 2 late in pregnancy. Whether this is on the basis of spasm or sclerosis is difficult to determine.

If, early in pregnancy, the A-V ratio is found to be 1 to 2, or between 1 to 2 and 2 to 3, even though the blood pressure is usually normal and continues to be normal month after month, nevertheless, one may predict that a moderate hypertension will occur during the last four to six weeks of pregnancy.

That this behavior of the blood pressure can be predicted and does occur may be seen from an analysis of 286 consecutive cases in which a retinal examination was done early in pregnancy. Table I shows the results of this analysis.

Table I may be summarized in the following statements:

1. In a series of 286 consecutive cases examined early in pregnancy, about one-sixth showed slight to moderate disturbance in A-V ratio, even though the blood pressure at that time was normal.

2. Of the patients showing normal A-V ratio early in pregnancy, about *one-fourth* developed hypertension four to six weeks before term; the remainder maintained normal blood pressure.

3. Of the cases showing disturbed A-V ratio early in pregnancy, about *two-thirds* developed hypertension four to six weeks before term. About nine-tenths of these were apparently due to vascular disease and showed no serious manifestations.

4. True toxemia, as shown by clinical symptoms, arterial spasms and toxic placental infarcts, was three times as frequent in normal A-V ratio cases as in disturbed A-V ratio cases, developing hypertension late in pregnancy.

TABLE I. 286 CONSECUTIVE CASES RETINAL EXAMINATION EARLY AND LATE IN PREGNANCY

(64 per cent below 30 years of age and 86 per cent showing diastolic blood pressure below 70 mm. mercury)

(A) 239 Cases (83.6 per cent) showed normal A-V ratio (2-3).

- (a) 179 Cases (74.9 per cent) maintained normal blood pressure to term. (Diastolic blood pressure not above 80 mm. mercury.)
- (b) 60 Cases (25.1 per cent) developed hypertension four to six weeks before term (diastolic above 80 mm. mercury).
  - (1) 9 Cases (15 per cent) showed apparent change from normal A-V ratio to between 1 to 2 and 2 to 3 during pregnancy—vascular disease?
  - (2) 22 Cases (36.7 per cent) proved true toxemia (Art. spasms and toxic infarcts).
  - (3) 29 Cases (48.3 per cent) presumably very mild toxemia (retinal and placental examination either negative or not done).

(B) 47 Cases (16.4 per cent) showed disturbed A-V ratio between 1 to 2 and 2 to 3, occasionally 1 to 2, seldom 1 to 3.

- (a) 17 Cases (36.2 per cent) maintained normal blood pressure to term.
- (b) 30 Cases (63.8 per cent) developed hypertension four to six weeks before term.
  - (1) 26 Cases (86.7 per cent) proved vascular disease (absence of Art. spasms and toxic infarcts).
  - (2) 4 Cases (13.3 per cent) proved true toxemia (presence of Art. spasms and toxic infarcts).

In other words, if the blood pressure was normal early in pregnancy, but the A-V ratio was slightly disturbed (between 1 to 2, and 2 to 3 or even 1 to 2) approximately *two-thirds* of these cases developed mild to moderate hypertension in the last four to six weeks of pregnancy, in contrast to only *one-fourth* of the cases having normal A-V ratio early in pregnancy. The hypertension in the disturbed ratio group did not exceed 150/95 unless there was a superimposed true toxemia, and was usually not in excess of 135/90. The incidence of true toxemia in the normal A-V ratio group was approximately three times as high as in the disturbed A-V ratio group, the hypertension in the latter being apparently on the basis of vascular disease.

In the above series of cases, the evidence of vascular disease was of a mild degree, yet it was associated with significant elevation of blood pressure and albuminuria in the last four to six weeks of pregnancy. When vascular disease is present to a more severe degree, certain other characteristics serve to differentiate it from true toxemia. It is important, therefore, to contrast the two conditions.

Hypertension, present early in pregnancy or arising later in pregnancy, is interpreted on the basis of vascular disease or true toxemia according to the following behavior and characteristics.

1. If, on retinal examination early in pregnancy, there is evident disturbance in the A-V ratio, varying from 1 to 2 to 2 to 3, or 1 to 2 up to 1 to 3, 1 to 4, or more, it is evident that the pregnancy is complicated by vascular disease. The more marked the disturbance in A-V ratio, the earlier the onset of hypertension in pregnancy and the more marked the increase in light reflex and A-V compressions. Hemorrhages and exudates are usually not seen unless the disturbance is

severe and of long standing, with associated kidney involvement. Localized arterial spasms are not seen unless there is a superimposed toxemia.

Hypertension due to true toxemia rarely occurs as early as the fifth month but becomes increasingly frequent after the seventh month. The A-V ratio is normal and the arterial spasms, at first sharply localized, become spindle-shaped and elongated with the increasing hypertension until, in severe cases, there is generalized constriction and the A-V ratio becomes much disturbed. Since the disturbed ratio is due to spasm rather than sclerosis, there is no corresponding increase in light reflex or A-V compressions, which helps to rule out vascular disease.

2. Edema, headache, and albuminuria are much less pronounced in vascular disease than in true toxemia with a comparable elevation of blood pressure.

3. Following the initial rise in blood pressure and appearance of albumin, subsequent observations at weekly intervals show very gradual increase in hypertension and albumin in vascular disease from week to week, as compared to true toxemia. Superimposed true toxemia causes rapid increase in edema, headache, hypertension, albuminuria, and the appearance of arterial spasms, the final evidence being found in the placenta as acute placental infarcts.

4. The more severe cases of vascular disease, which occur much more frequently among colored than white women, usually show a striking and unexplainable response to rest in bed. One frequently observes a blood pressure of 180/100 return nearly to normal after several days' rest in bed. An immediate return to the former high level is noted when the patient again resumes the upright position, even though she carries on no physical exertion. These cases also show marked fluctuation in blood pressure from day to day for no apparent reason.

In contrast to this behavior, hypertension due to true toxemia is not much influenced by rest in bed or indeed by any other measures. It remains persistently elevated and tends to increase. Edema may lessen with rest in bed but headache and albuminuria increase. Arterial spasms, at first sharply localized, become spindle-shaped, elongated, and finally produce generalized constriction. Hemorrhages in the retina may occur. Finally, examination of the formalin-fixed placenta shows the acute types of toxic infarcts.

5. The concentration test on the urine and the blood chemistry values are seldom affected in either vascular disease or toxemia of pregnancy, unless advanced cardiorenal disease or severe toxemia have seriously affected the kidneys. However, the uric acid value, which is usually normal in vascular disease, is definitely increased in toxemia, due probably to increased liver damage in the latter.

6. Hypertension and retinal changes due to vascular disease persist throughout the puerperium and show a gradual tendency to increase. This is likewise true of toxemia, if expectant treatment is followed, induction of labor delayed, and the patient subjected to long-continued

harmful effects on her vascular system and liver. In such cases, hypertension and albuminuria usually persist and subsequent observations show the patient has acquired vascular disease. However, it is well recognized that marked hypertension due to fulminating toxemia, subsides quickly after spontaneous or induced labor, and apparently leaves the patient none the worse for the experience.

7. Finally, examination of the formalin-fixed placenta from cases of hypertension due to vascular disease, shows no infarcts of the toxic types, namely the "C," "D," "E" and possibly the "B" types.[3] If infarcts of these types are present, they are proof of the toxic origin of the hypertension.

It is therefore apparent that in examination of the retina and the formalin-fixed placenta, we have the means of more accurate diagnosis and classification of cases of hypertension during pregnancy. If one finds a distinct disturbance in A-V ratio early in pregnancy, he is forewarned of the probability of development of hypertension in the latter part of pregnancy. The extent of the increase and the stage of pregnancy at which it will appear are directly proportionate to the degree of disturbance in the A-V ratio. Examination of the formalin-fixed placenta serves as a check in the final classification of the nature of the hypertension. Type "A" infarct (white) is nontoxic; Type "B" (yellow) is usually associated with slight hypertension and albuminuria; Type "C" (brown yellow) is associated with moderate toxemia; Type "D" (brown) is associated with severe toxemia and Type "E" (black) is associated with acute or fulminating toxemia.[3]

It must be remembered that true toxemia may be so mild that, except for a slightly greater degree of albuminuria and edema, it may simulate the picture above described as due to vascular disease with slight disturbance in A-V ratio. Failure to appreciate the fact that mild vascular disease may simulate mild toxemia in the last six weeks of pregnancy was responsible for the fact that in a former study of "unknown placentas"[3] a majority of the errors was made in this class of cases. The case was judged, clinically, to be one of mild toxemia but was classed as an error since toxic type of infarct was not found. We would now recognize such a case as one of mild vascular disease with the evidence now obtainable by retinal examination.

Briefly, therefore, the development of mild hypertension and albuminuria in the last four to six weeks of pregnancy may be due to (1) mild vascular disease, (2) Type "B" or "C" infarcts, or (3) Type "D" or "E" infarcts. The first two show a slow progression from week to week, whereas the third progresses rapidly, even within a week. Knowledge that the hypertension is on the basis of vascular disease lessens the physician's concern, but should not lessen his watchfulness.

Stander[4] recognized mild cases of albuminuria and hypertension in the latter part of pregnancy, which he classified as "low reserve kidney" rather than true toxemia. This type of case has since been the subject of much controversy, and the trend of opinion by other authors has been to regard these manifestations as indicative of a very mild toxemia. With the evidence obtained by retinal and placental examinations, we feel that these cases should remain in the category of low

reserve kidney, provided retinal examination shows evidence of vascular disease and placental examination shows no infarcts of the toxic types. This view presupposes that the kidneys show a similar, if not greater, degree of vascular disease.

We therefore venture to predict that when the types and significance of placental infarcts are more generally recognized, and the value of retinal examination in pregnancy is appreciated, there will result not only more uniform statistics concerning pregnancy complicated by toxemia and vascular disease, but more rational management of pregnancy when complicated by these conditions.

CONCLUSIONS

1. Examination of the retina and the formalin-fixed placenta are of fundamental importance in the interpretation of blood pressure behavior during pregnancy and the puerperium.

2. *Two-thirds* of patients showing mild to moderate disturbance in A-V ratio of the retinal vessels early in pregnancy, develop mild to moderate hypertension and albuminuria four to six weeks before term.

3. This behavior is on the basis of vascular disease, progresses very slowly and seldom requires interruption of pregnancy.

4. The greater the disturbance in A-V ratio, the more marked the increase in arterial light reflex and A-V compressions, the greater the hypertension and the earlier in pregnancy it arises.

5. Only *one-fourth* of patients showing normal A-V ratio early in pregnancy develop hypertension and albuminuria four to six weeks before term. True toxemia is relatively greater in this group than in the disturbed ratio group.

6. Hypertension, due to vascular disease, is accompanied by less edema, headache, albuminuria and blood uric acid increase and is more responsive to rest in bed than that of true toxemia.

7. Arterial spasms indicate true toxemia, and if found in connection with disturbed A-V ratio, increased light reflex and A-V compression, indicate true toxemia superimposed on vascular disease.

8. Hypertension due to toxic types of placental infarcts may simulate that due to vascular disease but can be differentiated not only by the clinical course but by retinal examination. Final proof rests upon examination of the formalin-fixed placenta.

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DISCUSSION ON PAPERS BY DRS. PECKHAM, BARTHOLOMEW AND COLVIN

DR. EDWARD D. ALLEN, Chicago, Ill.—Early recognition of vascular spasm as a prognostic sign should not only aid us in safeguarding our patients prenatally, but, as Dr. Peckham has stressed, should assist in the prognosis of an existent, as well as a future pregnancy. The appearance of recognizable vascular spasm early

in pregnancy, coupled with its continuation in the postnatal period, indicates a profound and sometimes permanent disturbance of the equilibratory apparatus of the vascular system.

A similar, though local, vascular spasm to the point of tissue necrosis has been nicely demonstrated by Dr. Harold Jones and his co-workers, in the menstrual endometrium and also in the decidua of ectopic pregnancy. This local damage is almost surely produced by changes in hormonal balance. It would seem reasonable to me to believe that the general vascular spasm of toxemia may be due to a more profound and lasting glandular imbalance.

Stability of glandular balance may determine the incidence of toxemia, while the ability to readjust the balance, when the disturbance is removed, should determine prognosis post partum and in future pregnancies. Dr. Peckham has shown the course of this readjustment during the period of involution.

Dr. Bartholomew has for years stressed the importance of degenerative changes in the placenta as a cause of toxemias. To me it seems more probable that the changes in the placenta are an additional example of disturbed physiology rather than an etiologic factor.

Yet I agree with Dr. Bartholomew in general that the placenta is probably the cause of toxemia. As soon as the placenta begins to function as a gland of internal secretion, toxemias such as vascular spasm, disturbance in glucose metabolism, in appetite, in water balance, and in glandular activity appear. As soon as the placenta dies or is removed, readjustment begins. Evidence, such as that produced by Drs. Smith, White, and co-workers, suggests that abnormalities in hormonal production, excretion or metabolism are a part of the toxemias of pregnancy.

A summary of these factors would suggest that the sudden impact of the tremendous quantities of hormones produced by this large, new and very active gland of internal secretion, the placenta, produces toxemia in those individuals who are unable to adjust themselves to it. The increased incidence of toxemia in association with the million units of prolan or the high levels of estrin excreted in twenty-four hours by the hydatidiform placenta is corroborative evidence. A considerable number of these unstable individuals are unable completely to readjust balance when the disturbing element is removed by delivery, and the residual scars of toxemia probably result.

DR. PHILIP F. WILLIAMS, PHILADELPHIA, PA.—The preceding papers contain two important points for consideration, namely: the early examination of the eye grounds in pregnant women as a newer diagnostic as well as a differential diagnostic sign; and a therapeutic suggestion in bringing to our attention the ultimate danger involved in permitting a toxemic woman to continue such a pregnancy over a certain period of time.

Dr. Bartholomew in discussing the arteriovenous ratio in the fundus of the eye may have found the solution to the problem which Dr. Peckham brings up in his paper. This is concerned with the question of whether particular vascular conditions antedate pregnancy. Routine use of the ophthalmoscope early in every pregnancy may throw some light on the further course of that pregnancy.

The examiner of the eye in pregnancy should be especially interested in the significance of changes in the caliber of the vessels. Experience may assist us to distinguish between the arteriolar sclerosis antedating pregnancy and the arteriolar spasm which is a part of the generalized phenomena in the specific toxemia of late pregnancy.

Dr. Peckham has stressed the relationship between the duration of toxemia and the ultimate changes found in the vascular system. In reviewing the histories of some 400 toxemic maternal deaths which occurred in the last ten years in Philadelphia, we obtained information that compared fairly closely with his as far as parity, previous toxemia, and the importance of a high diastolic pressure. In the Philadelphia series, the specific toxemias were most frequent in young primiparas, especially obese women or those with a suggestion of endocrine dysfunction; while the chronic hypertensive lesions appeared more frequently in the older, multiparous women. Over half of our 400 patients who died of toxemia gave a history of

previous toxemia, stillbirth, or repeated abortions. In a large number of the cases, the fatal outcome followed too long an attempt to carry the fetus to a viable period.

From his conclusions, a toxemic pregnancy should not be permitted to continue longer than four weeks if we are to avoid subsequent vascular damage. In many instances a choice will have to be made by the family between a possible live baby and a subsequently damaged woman with a necessarily shorter expectancy of life. From his findings the point may be raised as to whether the majority of toxemic women should be sterilized at or subsequent to the time of delivery.

With premarital physical examinations and evidence of negative syphilis an essential for marriage in many States, it seems to me that we have an excellent opportunity to determine the fitness of many women for reproduction. With pre-conceptional examinations including eye grounds, we may be able to determine and warn patients who are poor risks against the dangerous strain of a pregnancy.

DR. ROBERT D. MUSSEY, ROCHESTER, MINN. (by invitation).—The incidence of recognized toxemia of pregnancy among the obstetric patients at the Mayo Clinic has been about 5 per cent. Fifty-seven per cent of those patients, who had one or more subsequent pregnancies, had recurrence of the toxemia. It is evident that in many of these cases there were unrecognized vascular changes.

The hypertension of the toxemias of pregnancy is on the basis of vascular spasm in the presence of a toxic factor in the circulating blood. There seems to be direct ratio between the degree of hypertension, which indicates the severity of toxemia, the length of time this toxemia is imposed on the vessels, and the extent of degenerative vascular injury and of ensuing chronic cardiovascular-renal disease. High blood pressure is not, however, necessarily followed by vascular injury, since hypertension from hyperthyroidism, for example, is not commonly followed by vascular damage.

In cases of acute toxemia, spastic and other changes in the retinal arterioles furnish a valuable index of the degree of injury to the general vascular system. Repeated examinations reveal the rate at which this injury progresses. The presence and extent of changes in the retinal vessels may thus be helpful in determining if and when to terminate pregnancy.

When the patient is seen for the first time in the latter part of pregnancy, and has a mild elevation of blood pressure, it is sometimes difficult to determine whether the slight narrowing of the vessels, referred to by the authors, indicates previous vascular disease or a manifestation of the vasospasm accompanying early toxemia. Routine examination of the retinal vessels in the early months of pregnancy would undoubtedly establish a better basis on which to judge changes which may occur when the patient is examined later or when hypertension is present.

DR. J. HOFBAUER, CINCINNATI, OHIO (by invitation).—The recorded experimental and biochemical data warrant the conclusion that the various manifestations of pre-eclampsia bear a close resemblance to the morbid state produced by vasopressin (Byrom, Knepper, Gollwitz). The natural secretion of vasopressin may reach toxic levels if inadequately opposed by a pitressin-inhibitory substance. The existence of an inhibitor was surmised by Byrom, Teel, and Page.

I believe that acetylcholine, which is found in a considerable quantity in the normal human placenta (Dale, Gaddum, Hauptstein, Loeschke) and which acts as a powerful vasodilator, is a balancing force, designed to restrain forces favoring vascular hypertonia. Hyperfunction of the endocrine glands (thyroid, adrenal cortex, anterior pituitary), abundance of sex hormones in the blood, and the impairment of the excretory function of the liver represent the factors augmenting vascular tone.

Our findings of low levels of acetylcholine and increased levels of acetylcholine esterase in placentas of patients with severe toxemia and notably low choline values in the blood of pre-eclamptic and eclamptic patients point to a derangement of placental function. This placental deficiency is probably related to placental acute infarction and autolysis.

DR. WILLIAM J. DIECKMANN, CHICAGO, ILL.—Dr. Peckham states that if the toxemia lasts for four weeks or longer the patient is, in the vast majority of

cases, likely to have a chronic vascular disease. The concept that we have been using since 1933 is that the patient who can be carried for four weeks or longer with definite evidence of toxemia is, in most instances, a patient with hypertensive disease. We have not been able to carry patients with definite pre-eclampsia for periods of four weeks or longer. Because of the threatening symptoms, we have had to terminate the pregnancy.

Dr. Bartholomew's report that pathologic eye ground findings are present in patients with normal blood pressure is unusual. Furthermore, his statement that a high percentage of these patients subsequently develop hypertension is important. If confirmed, it gives us another test, in addition to the cold pressor test, to detect those patients who may develop toxemia.

DR. HOWARD C. TAYLOR, JR., NEW YORK, N. Y.—Dr. Bartholomew presented a list of the criteria which he believes help to separate the chronic vascular diseases from true toxemia. I want to report to you one additional criterion, based on a group of kidney function tests that we have been applying to the toxemia problem at New York University. These are renal clearance tests but made with special substances, one of which, inulin, measures glomerular filtration, while the other, diodrast, is a measure of renal blood flow. Tests of kidney function with these substances indicate striking differences in the patients with true toxemia and those with essential hypertension.

Nonpregnant patients with essential hypertension subjected to these renal clearance tests show signs of having a diminished renal blood flow and probably a constriction of the efferent arteriole to the glomerulus. A study of the patients with pre-existing hypertension in pregnancy indicates that in general these patients follow the pattern that is found in nonpregnant patients. On the other hand, those that develop symptoms only in the last trimester of pregnancy, i.e., patients with specific toxemia or pre-eclampsia, give no evidence of diminished blood flow, but perhaps some diminution in the rate of glomerular filtration. Later, after delivery, if these toxemic patients develop a persistent hypertension, then the kidney function tests are identical with those of essential hypertension in nonpregnant women or in men.

Dr. Peckham opened an interesting question when he said that, in regard to ultimate prognosis, the duration of time during which the patient suffered from toxemia was more important than the period of pregnancy at which these symptoms appeared. Now there are two concepts of the relationship of toxemia of pregnancy to hypertension. According to one view the toxemia is a special response of an already predisposed patient to the usual strains of pregnancy; according to the other there is a true toxemic process developing only during pregnancy and producing the damage to kidney and blood vessels that results in permanent hypertension. It seems to me that if specific toxemia were simply the development of symptoms on the basis of a pre-existing disposition to vascular disease, then the person with the greatest predisposition would exhibit this symptom earliest in pregnancy, so that the time of onset would be of most importance in ultimate prognosis. On the other hand, if the subsequent hypertension were due to damage resulting from an acute toxic process, then the duration of time during which the patient's organs were subject to these toxic effects would be most important in determining the probability of later chronic hypertension. Dr. Peckham's results seem to me to support the latter concept, and I am anxious to hear whether he believes this also.

DR. PECKHAM (closing).—I am still completely at a loss as to whether chronic vascular damage develops in patients previously susceptible to this condition or whether the process results from the toxemia itself. Many people have made vigorous attempts to prove that in those individuals later showing chronic vascular damage a subliminal condition was previously present but had not been diagnosed. However, so far as the studies which I have observed are concerned, it has seemed to me that in most instances, excepting those patients with obvious vascular disease antedating pregnancy, an arteriolar spasm develops and if that spasm is carried on over a certain period of time actual sclerosis results due to interference with the vascular supply of the vessels themselves. In other words, I am inclined to feel that chronic damage is the result of so-called pregnancy toxemia rather than a pre-existing disease.

DR. BARTHOLOMEW (closing).—In studying these cases of mild vascular disease developing hypertension late in pregnancy, we wondered whether they fell into the class that Dr. Stander called low reserve kidney. They do conform to that class as far as mildness of the symptoms is concerned. He found, however, that cases classed as low reserve kidney did not tend to recur, whereas many cases in our series did manifest the same behavior in subsequent pregnancies.

Whether one regards the placental infarcts as the cause or the effect, they are nevertheless very consistently associated with toxemia of pregnancy. When one finds the acute or subacute types of placental infarcts, the case must be regarded as one of true toxemia. If vascular disease is also present, toxemia is superimposed, and is an independent condition.

ENDOCRINE FACTORS IN SECONDARY AMENORRHEA*†

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THE numerous factors responsible for the occurrence of secondary amenorrhea have made it very difficult to develop practical clinical classifications and to determine correct therapeutic indications. It is desirable, therefore, to accumulate as many data as possible from these patients in the hope that they may eventually yield the necessary information. For this purpose our report is based on a statistical analysis of certain observations made on 73 selected clinic patients in whom no clear-cut cause for the disturbance could be found. The features studied consisted of (1) age, (2) duration of amenorrhea, (3) past history, (4) menarcheal age, (5) previous menstrual history, (6) fertility, (7) body weight, (8) basal metabolic rate, (9) assays of estrogenic and gonadotropic hormones in the blood, and (10) prognosis in an untreated group.

Many of the causes of secondary amenorrhea are found in definite organic lesions, such as tumors of the anterior hypophysis, adrenal cortex, or ovaries, or are associated with clinical entities, for example, tuberculosis, diabetes mellitus, severe malnutrition, psychic disorders. In most of the other cases it has been said that a differentiation usually may be made according to the endocrine gland chiefly involved and they are grouped under such diagnoses as primary or secondary anterior hypophyseal, adrenal, or ovarian failure. This method of approach is laudable and is practicable when the findings leave no doubt, but in most patients seen by the gynecologist the evidences of the endocrine disorder are variable and uncertain and demand both imagination and a rare diagnostic acumen for an unquestionable verdict.

The 73 patients of our series represent a selected group in whom the exact etiologic factor could not be determined in spite of careful clinical and laboratory investigation, and for that reason we believe that they are sufficiently homogeneous to allow a general comparison of the various points we have studied. This report is considered as a preliminary review of the series as a whole, and it is hoped in the future to correlate more closely the findings in the different groups.

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Our thanks are due to Dr. Horace Gray for his assistance with some of the mathematical analyses used in this study.

AGE

The patients selected were less than 35 years of age at the time their menses ceased, and in every instance at least one year had elapsed following the menarche. It was hoped in this way to avoid the inclusion of problems peculiar to early menstrual life and the premature appearance of the menopause. The range was from fifteen to thirty-eight years when estimated according to the age at the time of the first visit to the clinic, and from fifteen to thirty-five years when considered from the age of onset of the amenorrhea. The distribution was as follows:

AGE	FIRST VISIT	ONSET AMENORRHEA
15 to 19	12 cases	15 cases
20 to 24	18 cases	20 cases
25 to 29	25 cases	22 cases
30 to 35	15 cases	16 cases
35 to 38	3 cases	

DURATION OF AMENORRHEA

The duration of the amenorrhea varied from six weeks to ten years, this information being obtained from the patients' statements at their first visit. Since most of them were subsequently observed for periods of a few weeks to several months without menstruating, the actual duration was considerably longer in most instances. Some of the cases also should be considered as representing "oligomenorrhea" or "recurring periods of amenorrhea," and they have been included in order to give the correct perspective to our analysis of the preceding menstrual history. For the sake of convenience they may be subdivided into 5 categories, according to the length of the amenorrheic period:

6 weeks to 10 weeks	13 cases
11 weeks to 18 weeks	19 cases
19 weeks to 30 weeks	17 cases
7½ months to 18 months	13 cases
1½ years to 10 years	11 cases

PAST HISTORY

In selecting the patients for this series, a number were excluded because of acute or chronic illnesses which often are associated directly or indirectly with the occurrence of amenorrhea. We eliminated instances of pulmonary tuberculosis, diabetes mellitus, pituitary adenoma, chlorosis, tuberculosis of the spine, cephalothoracic lipodystrophy, rigid diet for reducing, amenorrhea subsequent to mumps, and ovarian arrhenoblastoma. Among those included, however, were 2 patients in whom the period of amenorrhea had its onset following abortion and in 5 instances of long duration it followed a full-term pregnancy. In addition, it is of interest that 11, or 15 per cent, of the group gave a history of a previous pelvic operation, although the relationship of this fact to the incidence of secondary amenorrhea is not clear. In 4 cases the operation consisted of a unilateral salpingo-oophorectomy, and there were one instance each of appendectomy and unilateral salpingectomy, tubal sterilization, appendectomy and suspension of the uterus, bilateral salpingectomy, cesarean section, cesarean section and tubal sterilization, and one of an unknown nature but which was not a bilateral oophorectomy or hysterectomy.

THE MENARCHE

The statement frequently has been made that a delayed onset of the menses is often found in women with oligomenorrhea and secondary amenorrhea. In order to determine this point the age at the menarche of the patients of this series has been compared with those of a group of normal Californian women. This control series is composed of 154 obstetric patients observed in our clinic in 1931 (Hotelling[1]). The actual figures are given in Table I.

TABLE I. FREQUENCY DISTRIBUTION OF THE MENARCHEAL AGE OF 73 PATIENTS WITH SECONDARY AMENORRHEA AND A CONTROL GROUP OF 154 NORMAL WOMEN

AGE (CENTRAL)	CONTROLS		AMENORRHEA	
	NUMBER	PER CENT	NUMBER	PER CENT
9.5	0	0	1	1
10.5	3	2	1	1
11.5	12	8	10	14
12.5	15	10	8	11
13.5	59	38	17	24
14.5	27	17	21	29
15.5	19	12	3	4
16.5	13	8	10	14
17.5	3	2	1	1
18.5	3	2	1	1
Total	154	100	73	100

The information used in studying both groups was obtained from the patients' statements and consequently is open to error, but nevertheless they are considered comparable. Since women generally give the "age at last birthday" when asked for their "age at the first menses" the half-year mark was used arbitrarily as the true point in computing the figures. When the different classes of the controls were plotted, the curve showed a normal Gaussian distribution, with the mean at 14.039 years, the standard deviation 1.593, and the standard error of the mean 0.128. The mean of the amenorrhea group was 13.925 years, slightly earlier than the controls, but the difference 0.115 years or 32 days is not considered as significant.

It may be stated, therefore, that in our series of patients with secondary amenorrhea no evidence was found to support the contention that such patients as compared to a normal group are more likely to give a history of a delayed appearance of the menarche.

PREVIOUS MENSTRUAL HISTORY

In contrast to the normal range of the menarcheal age found in this series is the large percentage of the subjects who complained of various menstrual disorders preceding the onset of the present illness (Table II). Since the records are necessarily based on the patients' recollections and not on carefully kept menstrual calendars, the actual figures are open to many errors.* Nevertheless, the trend is clearly discernible, since a

*When figures are obtained from case histories, as in this study, they cannot be compared with careful calendar records made by school girls, college students, or nurses such as have been published in recent years. Instead, they must be applied to data obtained in the same manner by interrogation of patients. For example, 27, or 18 per cent, of 154 obstetric patients on the Stanford service stated that they had "irregular menses" (Hotelling[1]), but a careful analysis of calendar records kept by a group of 76 nurses in the same institution showed an incidence of "irregular menses" of 63 per cent (Fluhmann[2]).

TABLE II. PREVIOUS MENSTRUAL HISTORY OF 73 PATIENTS WITH SECONDARY AMENORRHEA

I. Normal menses prior to amenorrhea		19
Except one previous period of amenorrhea (6 months or more)		4
Total		23
II. Menstrual disorder present since menarche		29
Oligomenorrhea	15	
Oligomenorrhea and hypomenorrhea	4	
Oligomenorrhea and hypermenorrhea	6	
Polymenorrhea	1	
Irregular menses, then hypomenorrhea	1	
Oligomenorrhea and hypomenorrhea, and at least one previous long period of amenorrhea	2	
III. Menstrual disorder for varying periods before onset of present amenorrhea		21
Oligomenorrhea	6	
Oligomenorrhea and hypomenorrhea	9	
Oligomenorrhea and hypermenorrhea	1	
Hypermenorrhea	1	
Hypomenorrhea	2	
Oligo- or hypomenorrhea and one previous long period of amenorrhea	2	

history of "normal, regular menses" was obtained in only 23 of the 73 subjects (32 per cent), and in 4 there had been at least one previous period of amenorrhea. In 50 (68 per cent) instances there was a history of some previous menstrual disorder, usually irregular delayed menses with or without hypomenorrhea or hypermenorrhea. In 29 subjects (39 per cent) the disturbance had been present since the menarche, while in 21 (29 per cent) it appeared for periods varying from a few months to several years before the onset of amenorrhea.

FERTILITY

It is obviously beyond the scope of this report to study in detail the obstetric history of the patients and its relation to the occurrence of amenorrhea, but Table III shows that, as a whole, they represent a "low fertility" group. Fifty of the 73 women were married, and 19 of

TABLE III. PREVIOUS OBSTETRIC HISTORY OF 73 WOMEN WITH SECONDARY AMENORRHEA

Not married*		23
Married		50
No pregnancies	19	
Married 11 months to 15 years	16	
Length of marriage not known	2	
Contraceptives	1	
Full-term pregnancies†	27	
Gravida i, Para i	9	
Gravida ii, Para i	5	
Gravida ii, Para ii	4	
Gravida iii, Para ii	2	
Gravida ii to vi, Para i to iv	5	
Gravida i, Para i, sterilized	1	
Gravida ii, Para ii, sterilized	1	
Incomplete pregnancies	4	
Gravida i, Para 0	3	
Gravida ii, Para 0	1	

*One patient had a previous induced abortion.

†Includes one patient, a nulligravida at the time of observation, who later had three pregnancies.

these had had no pregnancies, 27 had had one or more full-term pregnancies, and 4 had had one or two spontaneous abortions. Of the 19 with no pregnancies, it is known that 16 were married for from eleven months to fifteen years, used no contraceptives, and the majority mentioned sterility as a complaint when they came under our care. If this figure is taken as a minimum, it may be said that sterility occurred in 32 per cent or more of the whole group. Since the incidence of infertile marriages in the population at large is estimated at about 15 or 16 per cent, a low fertility was present in this series twice as often as in normal individuals. This finding is in keeping with Rubin's reported observations of women with oligomenorrhea and hypomenorrhea.[3]

BODY WEIGHT

It long has been recognized that extremes of body weight are important clinical accompaniments of secondary amenorrhea. In this series, the height and weight of 66 patients are known, and they have been compared with normal standard estimates obtained from the Medico-Actuarial Insurance Table.[4] For further study and comparison we selected a control group consisting of 100 women in the same age categories, with no gross pelvic disease and complaining of menorrhagia, metrorrhagia, polymenorrhea, dysmenorrhea, sterility, or habitual abortion (Table IV).

TABLE IV. FREQUENCY DISTRIBUTION OF INDEX OF BODY WEIGHT OF A SERIES OF 66 PATIENTS WITH SECONDARY AMENORRHEA AND A GROUP OF 100 CONTROLS

INDEX $\frac{\text{WEIGHT OBSERVED}}{\text{WEIGHT PREDICTED}} \times 100$	CONTROL SERIES	AMENORRHEA	
		NUMBER	PER CENT
200-204		1	1.5
195-199			
190-194		2	3.0
185-189		1	1.5
180-184			
175-179		2	3.0
170-174			
165-169			
160-164		1	1.5
155-159			
150-154	1		
145-149		1	1.5
140-144		1	1.5
135-139	2	3	5.0
130-134	2	4	6.0
125-129	1	3	5.0
120-124	1	2	3.0
115-119	5	5	7.0
110-114	9	4	6.0
105-109	8	4	6.0
100-104	7	4	6.0
95- 99	9	3	5.0
90- 94	18	8	12.0
85- 89	7	7	10.0
80- 84	17	3	5.0
75- 79	10	4	6.0
70- 74	2	2	3.0
65- 69	1	1	1.5
Total	100	66	100

The weights in each series were computed for the Index $= \frac{\text{Weight observed}}{\text{Weight predicted}} \times 100$. According to this calculation, a normal person should have an index of 100 and any number above this is an indication of overweight. A mathematical analysis of the figures shows that they are statistically significant and that there is a definite tendency toward obesity in amenorrheic women. The average for the control group was 96 and for the amenorrheic women 112. The index for 38, or 58 per cent, of the total number of women with amenorrhea was over 100 and a further glance at the table shows that 10 per cent of them were heavier than the heaviest of the controls with other menstrual disorders or sterility.*

BASAL METABOLIC RATE

One or more records of the basal metabolic rate in 66 of the 73 patients are available, and they support the contention of Haines and Mussey,[5] Litzenberg and Carey,[6] Frank and others,[7] that a lowered thyroid activity is often associated with diminished ovarian function. The range was between minus 27 and plus 21 per cent, so that no great extremes were observed, and there were no definite clinical instances of myxedema or hyperthyroidism. The rate varied within the normal range of plus 10 and minus 10 in 33, or 50 per cent, of the cases, while only 4, or 6 per cent, were more than plus 10, and 29, or 44 per cent, were below minus 10. These figures may be compared with those of 100 women in the same age categories, with no gross pelvic lesions and complaining of sterility, polymenorrhea, menorrhagia, metrorrhagia, or dysmenorrhea. In 58 (58 per cent) of this group the basal metabolic rate was between plus 10 and minus 10; in 12 (12 per cent) it was above plus 10; and it was between minus 10 and minus 24 in only 30 instances (30 per cent) (Table V).

TABLE V. FREQUENCY DISTRIBUTION OF THE BASAL METABOLIC RATE OF 66 PATIENTS WITH SECONDARY AMENORRHEA AND A GROUP OF 100 CONTROLS

BASAL METABOLIC RATE	CONTROL SERIES	AMENORRHEA	
		NUMBER	PER CENT
+21 to +19	0	1	1.5
+18 to +16	4	1	1.5
+15 to +13	1	0	0.0
+12 to +10	7	2	3.0
+ 9 to + 7	6	3	4.5
+ 6 to + 4	9	7	10.5
+ 3 to + 1	7	2	3.0
0	1	2	3.0
- 1 to - 3	12	7	10.5
- 4 to - 6	10	7	10.5
- 7 to - 9	13	5	8.0
-10 to -12	12	10	15.0
-13 to -15	10	7	11.0
-16 to -18	6	6	9.0
-19 to -21	1	2	3.0
-22 to -24	1	1	1.5
-25 to -27	0	3	4.5
Total	100	66	100

*In this study no allowance was made for hereditary influence. A more detailed analysis of body weight in a group of this type would necessitate serious consideration of racial factors. An appreciable proportion of the patients from the Stanford Clinic trace their origin to peoples bordering on the Mediterranean, and it is well recognized that their women comparatively early gain weight, with or without menstrual disorders.

Although it is not possible in this report to deal in detail with the treatment of patients with secondary amenorrhea, the results obtained in a group receiving solely thyroid extract by mouth is worthy of mention since it is strikingly in accord with the experiences of the authors mentioned in the preceding paragraph. Of 21 patients in this category, all of whom had low basal metabolic rates, 14 responded with regular cyclic bleeding, 1 became pregnant, 1 had a single period of bleeding while under observation, 4 remained amenorrheic, while 1 was not followed. It may be stated, therefore, that a so-called "cure" occurred in 15, or 71 per cent, of these patients, a result unequalled in other groups by any other means of therapy we have employed.

ESTROGENIC HORMONES IN THE BLOOD

The employment of tests for estrogenic hormones in the blood and urine of women with various disturbances of the menstrual cycle once gave hope that they might offer much assistance from the standpoint of diagnosis as well as therapy. Several extensive studies have been published, notably by Frank and his associates,[7] Siebke,[8] Mazer and Goldstein,[9] Fluhmann,[10] and Albrieux.[11] In each case the authors were able to classify amenorrheic patients according to the estrogen content of blood or urine, but these results have not received any interpretation that lends itself to practical application. They do not differentiate any definite endocrine entities and do not point to effective methods of treatment with available hormonal substances.

The estrogenic hormone content of the blood of 52 patients of our series was determined by the Fluhmann mucification test.[10, 12] The blood was examined weekly for from three to six successive weeks, and, as reported previously before this Society (Fluhmann[10]), the patients could be divided, according to results, into 3 categories. First was the so-called "cyclic" group in whom the level of estrogenic hormones reached a high or comparatively high concentration at intervals of two weeks or more. Second, repeated examinations of the blood showed a constant appreciable amount of the hormones from week to week. Third, estrogens were not demonstrable in the blood during the total period of investigation.

A periodic increase of the blood hormone was observed in 46 of the 52 patients studied, while repeated positive tests were noted in 4 instances and consistent negative results in only two. An analysis of the two smaller groups did not point to any specific individual characteristic or endocrine type associated with the endocrine behavior. This fact and the realization that cyclic estrogen curves also have been demonstrated by our procedure in castrate and postmenopausal women make us feel that this method of investigation does not offer any assistance in the care of women with secondary amenorrhea.

ANTERIOR LOBE GONADOTROPIN IN THE BLOOD

The demonstration of an excessive amount of anterior hypophyseal gonadotropic hormone in the blood long has been recognized as evidence of a total loss of ovarian function (Fluhmann[13]), and it is surprising that positive tests were obtained in only 7, or 20 per cent, of 34 patients of this series. This figure is in marked contrast to the occurrence of positive tests in from 65 to 80 per cent of women following castration

or the menopause. We also have noted the presence of unduly great amounts of this hormone in the blood of 5 out of 6 patients with primary amenorrhea.

Although it is not possible to draw conclusions from so few cases, an analysis of the 7 patients with positive tests indicates that the demonstration of an unduly large amount of anterior lobe gonadotropin in the blood should be considered as evidence of a serious or prolonged ovarian disturbance. As compared to the whole series they represent an older group, the youngest being 25 years of age. The period of amenorrhea was longer than seven and one-half months in all cases, and in 3 instances it was of three, four, and nine years, respectively. Five of the 7 patients had a lowered basal metabolic rate, two a delayed menarche (sixteen and seventeen years, respectively), and 3 were obese. Six of the 7 received treatment, but only 2 responded with cyclic uterine bleeding.

PROGNOSIS IN UNTREATED CASES

It is not the purpose of this report to discuss the therapy of secondary amenorrhea, but it is of interest to note the experience of 22 patients in this series who were under observation for some weeks or months and yet received no treatment. In 15 instances there was no change in the amenorrheic condition, but in 4 cases there occurred a single period of bleeding following which the patients failed to report, and 3 women experienced a return of cyclic uterine bleeding. Of these 7, only 2 had periods of amenorrhea of less than three months' duration and could be considered as merely examples of *oligomenorrhea* in whom an early reappearance of the menses could be expected, while in two the condition had been present for four and five years, respectively.

Any estimation of therapeutic measures employed in secondary amenorrhea must take into consideration that there is a certain incidence of spontaneous "cures." In this series 7, or 35 per cent, of a group of 22 patients had a period of uterine bleeding while they were under observation and before any treatment had been instituted.

SUMMARY

This report is based on 73 clinic patients with a secondary amenorrhea for which no definite cause could be ascertained.

The age of the patients varied from fifteen to thirty-eight years at the time of observation, and the duration of the amenorrhea from six weeks to ten years.

Amenorrhea set in after an abortion in 2 instances and after a full-term pregnancy in 5 cases. Eleven, or 15 per cent, gave a history of a previous pelvic operation.

The range and the mean of the menarcheal age showed no significant difference from a control group of normal women.

A preceding menstrual disorder, most often oligomenorrhea or hypomenorrhea, was noted in 50, or 68 per cent, of the whole group. In 29, or 39 per cent, the disturbance had been present since the menarche and in 21, or 29 per cent, it appeared for varying periods immediately preceding the amenorrhea.

Infertile marriages were present in over 30 per cent of the married women in the group.

A definite tendency to obesity was observed, since 38, or 58 per cent, of 66 patients were above the normal standard estimates of the Medico-Actuarial Insurance Table.

No clear-cut instances of marked hypo- or hyperthyroidism were included, but a basal metabolic rate of between minus 10 and minus 27 per cent was found in 29, or 44 per cent, of 66 cases.

The estrogenic hormone content of the blood was determined at weekly intervals in 52 patients. A cyclic increase in the hormone concentration was observed in 46 cases, while repeated positive tests were noted in 4 instances and consistent negative results in only two.

An excessive amount of anterior pituitary gonadotropin was present in the blood of 7, or 20 per cent, of 34 women. It is felt that this observation is evidence of a serious or prolonged ovarian disturbance.

A period of uterine bleeding appeared before any treatment had been instituted in 7, or 33 per cent, of a group of 22 patients.

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DISCUSSION

DR. HAROLD O. JONES, Chicago, Ill.—In interpreting his own work Dr. Fluhmann has made several pertinent, straightforward statements which should command the attention of all clinicians. He states:

1. That the estrogen content of the blood or urine does not differentiate any definite entities.

2. That quantitative determinations of the estrogen content in the blood or urine do not offer any assistance in the care of women with secondary amenorrhea. (These two statements, based on the work of several years, immediately gain favor, since it is obvious that the authors would be most desirous of attaching clinical significance to their experimental findings.)

3. That spontaneous cures in patients with secondary amenorrhea are frequent.

4. That thyroid therapy has been more beneficial than any of the other hormonal substances.

The quantity of anterior lobe gonadotropins in the blood seems to be significant in the differentiation between partial and more complete cessation of ovarian function. This, if borne out by histologic study of human ovaries, offers a test of clinical value.

My own observations of patients with secondary amenorrhea are in accord with the statement that the cycles in these patients prior to the onset of amenorrhea were not normal in the majority of instances. The balance between functional bleeding, irregular cycles, and amenorrhea is indeed a very delicate one.

There are several known facts that cause blood and urine assays to be of doubtful significance. The amount of sex hormones in the circulating blood is low. This is due to the fact that the liver has a tremendous ability to remove the hormones and change them to substances of very low or no potency. The methods of extracting these hormones from the blood have been very inefficient in the past. The blood

has not been hydrolyzed, and thus 30 per cent, or less, of the hormone has been recovered for assay. Due to the small number of animals used in the assays of such material, the percentage of error ranges from 100 to 10,000.

DR. JEAN PAUL PRATT, DETROIT, MICH.—In selecting clinical patients in whom no clear-cut cause for the disturbance could be found, one may question whether hypothyroidism has been excluded by the authors. In Table V, 73 per cent of the patients had a minus basal metabolic rate. In Table IV, 57.5 per cent of the patients were overweight. To what extent do these variations in the basal metabolic rate and weight coincide? Furthermore, 71 per cent of the patients with low basal metabolic rate were relieved of amenorrhea by the administration of thyroid. Other reports are cited showing that a lowered thyroid activity is often associated with diminished ovarian function. To eliminate known causes of amenorrhea, would it have been desirable to test the response to thyroid therapy in all the patients in this group? What symptoms are necessary to establish a diagnosis of mild hypothyroidism?

Would it be desirable to include diet in the investigation of the causes of secondary amenorrhea? Extreme malnutrition was assumed as an obvious cause of amenorrhea. Is it possible that lack of balance of proteins, carbohydrates, and fats, as well as a deficiency in vitamins, might be important factors though extreme variations in the apparent state of nutrition were not conspicuous?

It has been my practice for several years, when investigating menstrual disorders, to obtain from the patients an accurate record of the food ingested. These data are collected by giving each patient a form to complete. This form includes one column for the kind of food eaten and another for the amount. The patient is requested to continue her customary habits of eating and to complete a form each day for one week. From this information a dietitian computes the number of calories of fats, carbohydrates, and proteins, and estimates the vitamins. Conforming to the individual's taste, a few changes are suggested to restore a normal balance. By this means alone many menstrual disorders may be corrected.

The finding of so many (68 per cent) who complained of various menstrual disorders preceding the onset of the present illness, opens an important though difficult subject for further study. The story of progress in combatting disease usually follows a definite pattern: recognition of the conspicuous manifestations; observation of the less conspicuous symptoms; search for the cause of early symptoms; education of the profession; education of the laity to seek advice for the early symptoms and prevention. Increasing evidence tends to relate secondary amenorrhea to causes operating earlier and manifesting themselves by various menstrual disorders. One may even go further and suggest the relation of menstrual disorders to conditions existing before the menarche. Prevention may belong in the realm of the pediatrician. Gynecologists still have the problem of clarifying the causes of minor menstrual disorders and preventing them.

DR. EMIL NOVAK, BALTIMORE, MD.—It is refreshing to hear a man of Dr. Fluhmann's experience in this field present a paper stressing the limitations rather than the accomplishments in the management of amenorrhea.

As regards the amenorrhea due to defective nutrition, it has always seemed to me that these cases are in the final analysis due to ovarian hypofunction, for the ovaries are singularly sensitive to nutritional deficiencies. The mere withdrawal of certain vitamin principles from the diet of experimental animals, for instance, brings about an abolition of the cycle.

In the present state of our knowledge, no one can feel satisfied with efforts to classify the causes of this disorder. For practical purposes, however, we should try to distinguish etiologic groups as best we can, with full appreciation of the frequently unscientific basis for such division into pituitary, ovarian, thyroid, and other groups.

An interesting variety of amenorrhea is that seen at times following full-term delivery or miscarriage. Pregnancy is one of the critical periods in a woman's endocrine career, and it not infrequently involves a re-shuffle of endocrine factors. Functional bleeding rather frequently has its inception following pregnancy, while in other cases amenorrhea may develop. This is the so-called superinvolutional amenorrhea of the older gynecologists. Many women have an unsteady endocrine

balance. In a number of instances, with or without treatment, I have observed a cyclic tendency, characterized by alternating phases of functional bleeding and amenorrhea, over a term of years.

The real indication for treatment in a large proportion of cases is an associated sterility, especially as the amenorrhea in itself is harmless to the patient. On the other hand, we encounter an interesting group in which pregnancy occurs even when amenorrhea has been present for long periods of time, even a good many years. In such cases a typical endometrial cycle occurs, except for the bleeding phase. There is a curious lack of knowledge as to the histology of the endometrium in such cases, although it seems likely that the transition between the progestational and the postmenstrual stages is brought about by a simple involutional change, and is not associated with desquamation or bleeding.

DR. SAMUEL H. GEIST, NEW YORK, N. Y.—I would like to ask Dr. Fluhmann whether there was any correlation between the gonadotropic hormone findings and the estrogen findings?

DR. JENNINGS C. LITZENBERG, MINNEAPOLIS, MINN.—It is nineteen years since I promulgated the idea that basal metabolism was an important factor in all complications of menstruation. My first report in 1926 was only preliminary, but it is with considerable satisfaction that I note in Dr. Fluhmann's group reported today that the low basal metabolism figures agreed with mine almost exactly.

DR. FLUHMANN (closing).—I should have made it clear that this report is merely a preliminary study. When we started this work, it was our hope that the findings in the different groups could be correlated and possibly give us a clue to some sort of classification. However, the problem became far too complicated, and we offer these statistics now merely as observed facts.

Dr. Pratt's question with regard to hypothyroidism is a very embarrassing one, and I do not know just what to say. Certainly some of the patients were overweight and had a low basal metabolic rate. We decided finally to include them, but we eliminated individuals who were definitely myxedematous.

The question of diet was carefully considered, and no patient was included in whom there was definite evidence of malnutrition.

Two of the patients with excessive amounts of anterior pituitary gonadotropin in the blood also presented a cyclic rise in estrogenic substances.

The injection of estrogenic substances directly into the cervix uteri, which a discussant mentioned, is not a new procedure. It must be employed with caution and is not devoid of risks. The question came up recently during the course of a trial in California, and the doctor concerned was suspected of attempting to produce an abortion by means of such injections.

OSTEOCHONDRITIS IN THE STILLBORN*

JAMES R. MCCORD, M.D., ATLANTA, GA.
(From the Department of Obstetrics and Gynecology, Emory University School of Medicine)

CERTAIN skeletal changes in the fetus and newborn as seen by the roentgenogram are almost pathognomonic of congenital syphilis. When deviations that are not typical are called syphilis, this excellent method of diagnosis is discredited. Briefly, what are these typical changes? McLean, is one of his classical articles, says:

"There is a more advanced stage of the previous lesion (rarefaction) in which the roentgenologist can usually make an unequivocal diagnosis of osseous syphilis in the presence of negative serology and a history of a negative physical examination. The so-called zigzag or saw-tooth metaphysis type is not uncommon. Saw-tooth metaphyses are the first evidence of lawlessness of growth so characteristic of the active stage of syphilis, concerning which there has been so much controversy." As long as we make the diagnosis of syphilis upon such lesions we are on safe ground. To quote McLean again: "One should be warned against accepting the presence of one or possibly two minute spurs or buds shown on the metaphyses by the x-rays as evidence of syphilis, since they also occur in rickets. *True syphilitic types show a definite saw-tooth edge.*" (Italics mine.) Failure to heed the above was the cause of most of my failures. Caffey in a recent article says:

"In this non-syphilitic group no cases resembling the following *rarer* [italics mine] types of syphilitic osteochondritis were found: (1) saw-tooth metaphyses; (2) foci of rarefaction in the angles of the cartilage shaft junctions and multiple infarctions through the ends of the shafts."

Evans in a recent communication says: ". . . and there is no doubt that characteristic osseous lesions are found in a very high percentage of cases of fully developed syphilis. The diagnosis in the less obvious cases is more difficult and both positive and negative errors may be made."

In attempting to prove my point, I desire to present an analysis of roentgen ray studies on 129 negro fetuses at all stages of gestation, the great majority of them stillborn. The work has been done without an experienced and advanced radiologic or histologic background. It is an effort to show that the average doctor can confidently make the diagnosis of advanced congenital syphilis provided he does not split hairs in evaluating the lesions observed. The method of study follows: The diagnosis was made from the film without any knowledge of the case. If the films showed a positive or doubtful diagnosis, the babies were autopsied. The following tissues were stained by the Levaditi method: kidney, liver, spleen, lung, heart and thymus. The bone lesions were reported as syphilitic only when the organisms of syphilis were found in the stained tissues. The original Levaditi stain was used. It is essential that the method be meticulously followed. As an example, we failed to demonstate the organisms when neutral formalin was used in the place of acid formalin.

*Read at the Sixty-Sixth Annual Meeting of the American Gynecological Society, Colorado Springs, Colo., May 26 to 28, 1941.

In the entire series, the diagnosis of syphilis as made from the roentgenogram was confirmed by the finding of the organisms of syphilis in 91.5 per cent. There should have been but 1.6 per cent of incorrect

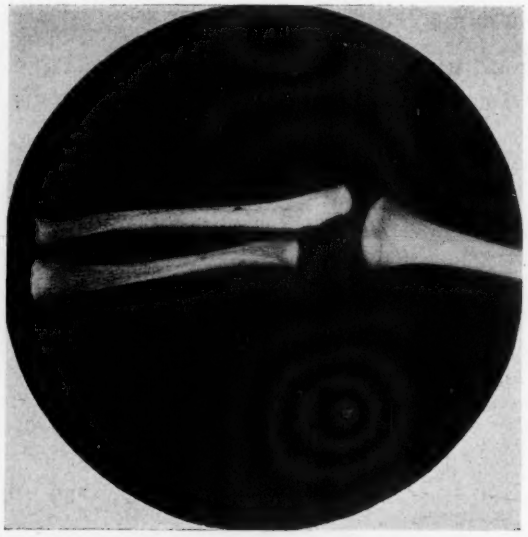

Fig. 1.—Abortion (1,070 Gm.), macerated; Wassermann and Kahn, 4-plus; no treatment; diagnosis, doubtful; organisms found. Probably not safe for average doctor to make diagnosis of so early a lesion.

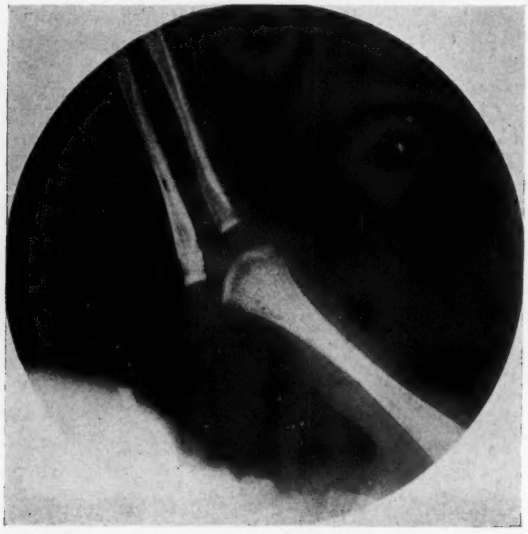

Fig. 2.—Abortion (610 Gm.), macerated; Wassermann and Kahn, 4-plus; no treatment; diagnosis, syphilis; organisms found. Probably as early a lesion as safe for average doctor to make positive diagnosis.

diagnoses. A review of the 11 films incorrectly diagnosed showed that 9 did not have the serrations or saw-tooth metaphyses upon which premise the study originated (Table I). One erroneous diagnosis was hazardous

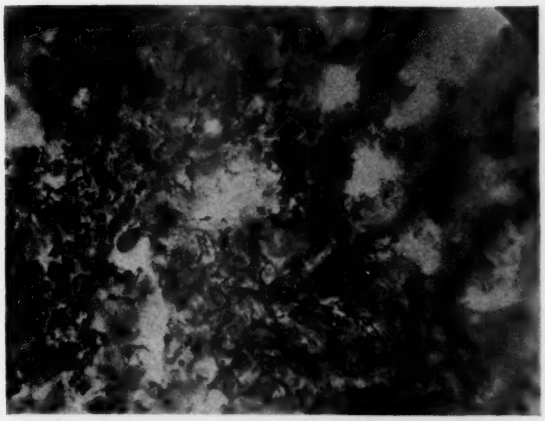

Fig. 3.—Innumerable organisms found in baby of comparatively early lesion of Fig. 2.

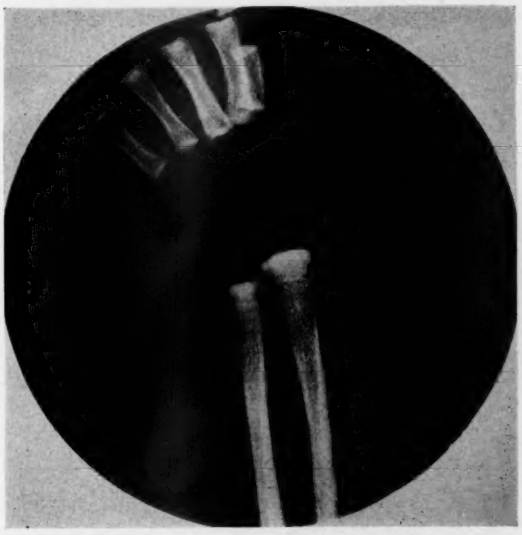

Fig. 4.—Term (2,820 Gm.), macerated; Wassermann and Kahn, 4-plus; no treatment; diagnosis, syphilis, organisms found. Comparatively early lesion, probably unsafe diagnosis for average doctor.

TABLE I. REVIEW OF MISSED DIAGNOSES

1. No serrations; plainly neg.	380 Gm.
2. No serrations; plainly neg.	400 Gm.
3. No serrations; plainly neg.	200 Gm.
4. No serrations; plainly neg.	1,400 Gm.
5. No serrations; plainly neg.	1,800 Gm.
6. No serrations; plainly neg.	2,030 Gm.
7. No serrations; plainly neg.	1,050 Gm.
8. No serrations; plainly neg.	240 Gm.
9. Confusing; again positive	600 Gm.
10. Confusing; not typical serrations	560 Gm.
11. Hazardous diagnosis; small fetus	320 Gm.

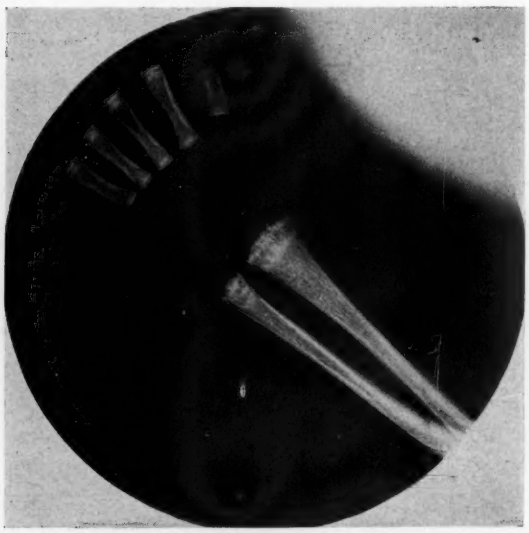

Fig. 5.—Premature (2,120 Gm.), macerated; Wassermann, 4-plus; no treatment; diagnosis, syphilis, organisms found; pathognomonic saw-tooth serrations, premise upon which this work was done.

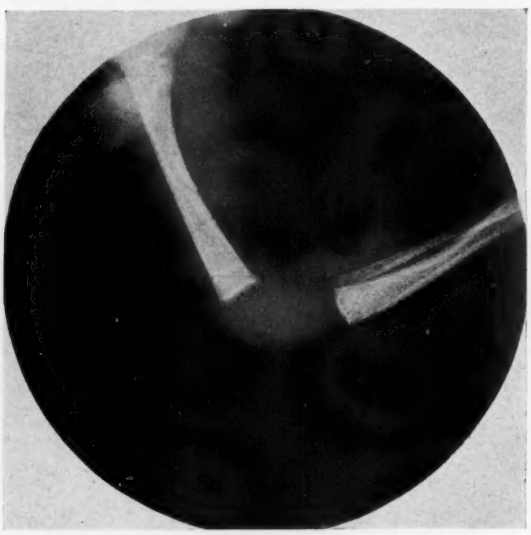

Fig. 6.—Abortion (400 Gm.); Wassermann and Kahn, negative; no treatment; diagnosis, developmental; organisms not found; minute spurs and buds not a safe diagnosis for a fetus of this size.

TABLE II. DIAGNOSES MISSED (11)

Wassermann-Kahn positive	2
Wassermann-Kahn negative	6
Tests agree	8
Wassermann positive	1
Kahn negative	2
Treated	2
Average weight (Gm.)	816
Serology positive	27%

in that the fetus weighed only 320 Gm. In only one was the lesion apparently typical and the organisms not found. Serology was positive in only 27 per cent of the mothers in this group. The average fetal weight was 816 Gm.

Fig. 7.

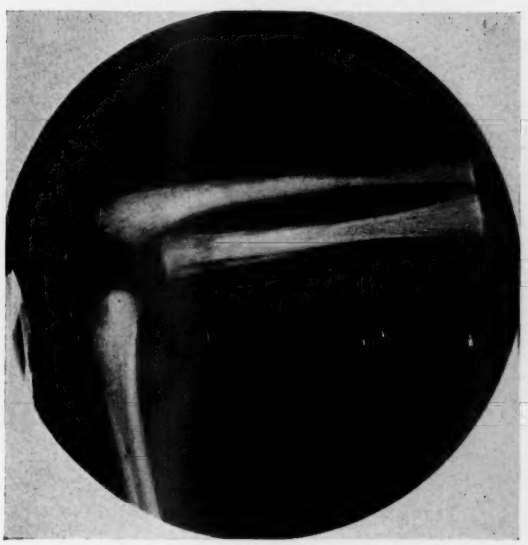

Fig. 8.

Figs. 7 and 8.—Premature (1,520 Gm.), not macerated; Kahn, 4-plus; no treatment; diagnosis, syphilis; organisms not found, even though lesions apparently far advanced.

The diagnosis of syphilis was made from 88 films and the organisms of the disease were found in the babies. The outstanding fact in this group is that 94 per cent of the mothers had positive serology. The average

fetal weight was 1,704 Gm. Only 16 of the women had received any treatment during pregnancy and the average number of treatments was two (Table III).

Fig. 9.—Abortion (890 Gm.), macerated; Wassermann and Kahn, 4-plus; no treatment; advanced lesion; organisms found.

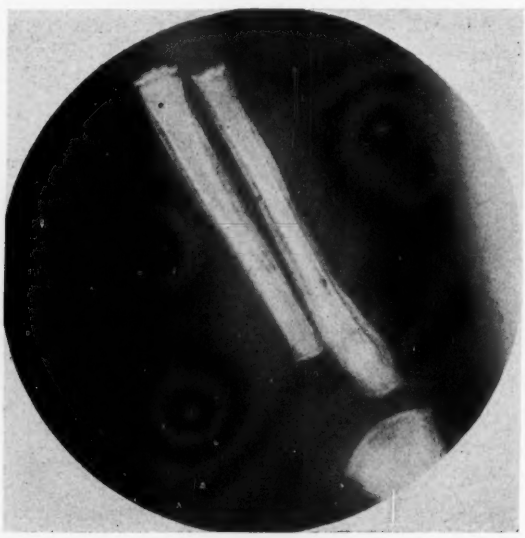

Fig. 10.—Premature (2,290 Gm.), stillborn, macerated; Wassermann and Kahn, 4-plus; diagnosis, syphilis; no treatment; organism found; serration, rarefaction, and periosteal elevation.

To compare the serology percentage, 321 negative films were reviewed. Maternal serology was negative in 80 per cent. Fourteen per cent were positive and the mothers received treatment during pregnancy. The average number of treatments was 8.3. Six per cent were positive with

no treatment. It seems justifiable to think that caution should be exercised in diagnosing congenital syphilis of the bones when the maternal serology is negative.

The serologic tests used were: a 3 tube Kolmer modification with serum dilutions of 0.05 and $\frac{1}{10}$, with icebox fixation and the standard Kahn. Both of these tests were done upon 76 mothers. There were only 3 discrepancies. It seems probable that this speaks well for the reliability of the tests during pregnancy.

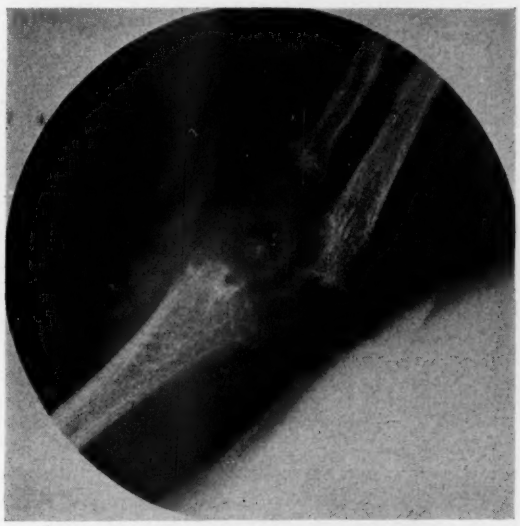

Fig. 11.—Rickets with periosteal elevation.

Twenty fetuses were so small that a diagnosis was not attempted. Their average weight was 229 Gm. The tissues were stained and the organisms of syphilis were not found in any of them. The maternal serology in this group was positive in 35 per cent. The average duration of pregnancy was approximately eighteen to twenty weeks. It is probable that an abortion happened in some of these women before intrauterine infection occurred. It is not wise to attempt the diagnosis of skeletal syphilis on fetuses of this size.

TABLE III. ORGANISMS FOUND

Number studied	88
Wassermann-Kahn positive	47
Wassermann-Kahn negative	3
Tests disagree (Wassermann neg.—Kahn pos.)	3
Wassermann positive	27
Wassermann negative	2
Kahn positive	6
Serology positive (%)	94
Treated	16
Average number treatments	2
Average weight (Gm.)	1,704

Nine diagnoses were doubtful. The typical serrations were not present. In two the organisms of syphilis were found, and the maternal serology was positive in 33.3 per cent. Only two mothers received any antepartum treatment. The average fetal weight was 1,754 Gm.

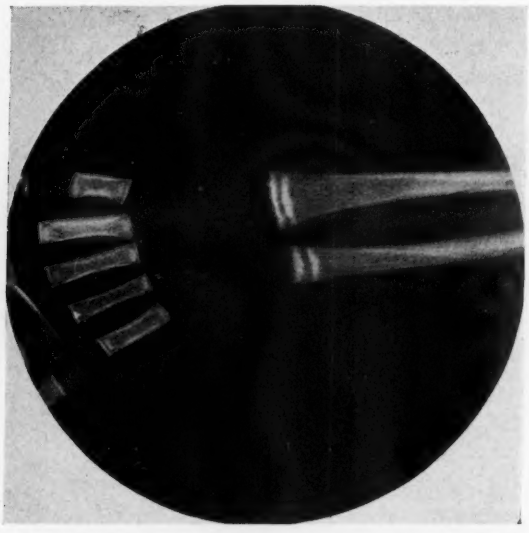

Fig. 12.—Aged 16, premature (1,500 Gm.), alive; Wassermann and Kahn, 4-plus; no treatment; diagnosis, syphilis; organisms found. Rather rare lesion probably pathognomonic.

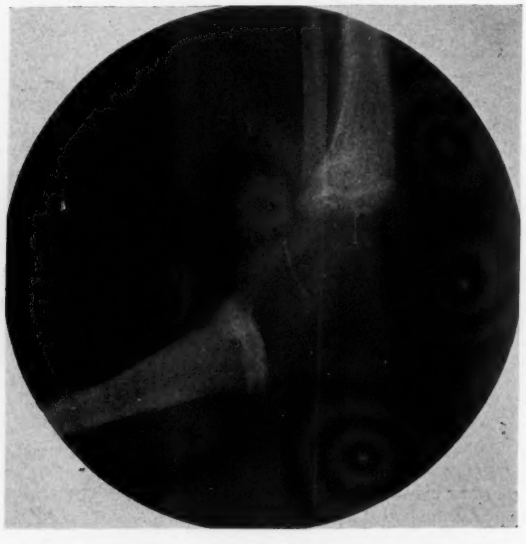

Fig. 13.—Other bones of same baby as in Fig. 12.

CONCLUSIONS

1. Typical saw-tooth serrations are pathognomonic of congenital syphilis.

2. Properly done Wassermann and Kahn tests should be positive in probably 90 per cent of the mothers of syphilitic babies.

3. It can be said, rather arbitrarily, that it is unwise to diagnose congenital syphilis by the roentgen ray in fetuses weighing less than 500 Gm.

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50 Armstrong Street

DISCUSSION

DR. GRANDISON D. ROYSTON, St. Louis, Mo.—It is generally recognized that syphilis and nephritis must be excluded or recognized as a cause in every stillbirth. It is further recognized that routine serologic tests are indicated as early as possible in every pregnant woman, while autopsies on all stillbirths are highly desirable. Yet often the autopsy reports of "autolysis of tissues," negative serologic reactions, etc., are discouraging. Dr. McCord's report denotes that the roentgenograms are the simplest means of diagnosing syphilis as the cause of fetal death.

Serologic reactions of cord blood are of doubtful value since the latter may carry complement fixation antibodies from the mother. These so-called "reagens" may disappear in from one to twelve weeks after birth, when the child's true status may be determined. Roberts believes if the infant reaches the age of four months without positive blood tests or physical evidence of the disease, it probably is not syphilitic. Jeans and Cooke have never found syphilis in an infant with no physical evidence of syphilis, whose Wassermann was negative at two months of age.

The qualitative Wassermann reaction on cord blood is of only minimal importance, but the quantitative determination of titer and comparison with subsequent blood tests seems of greater value. Placental study is of no importance if the mother has received treatment, for even inadequate treatment usually renders the placenta free from evidence of syphilis. I agree with the essayist in preferring the standard Kahn to the Wassermann test.

More than twenty-seven years ago, Ludwig Pick taught that osteochondritis of the long bones was pathognomonic of syphilis, yet it has been too frequently overlooked. Stokes reported that among more than 200 patients with syphilitic bone lesions, only 24 per cent had had serologic tests, while 82 per cent were found to be positive on examination. He emphasizes the necessity of skillful interpretation of the roentgenograms. Syphilis is a preponderantly constructive osteoplastic process, followed later by destructive changes.

Osteochondritis or periostitis in the syphilitic infant is limited to the first five months of the baby's life. It is usually observed at birth or during the first two or three months of life. It is important to remember that syphilitic bone lesions are always bilateral in the first months of life. According to Shands, the order of frequency of these lesions is: (1) the lower ends of the femur; (2) lower ends of the tibia and fibula; and (3) lower ends of the radius and ulna.

The cases of congenital bone syphilis in the St. Louis Children's Hospital from 1920 to 1938 were reviewed by Jostes and Roche of the Orthopedic Department. It is interesting to see that in their series of 34 cases, they found the tibia and fibula involved more than twice as often as the femur.

In the Washington University Clinic, among the last 8,571 obstetric admissions, 6,227 white and 2,344 negroes, 2.8 per cent of the white patients and 14.5 per cent of the negroes were syphilitic. The general incidence of pregnancy and syphilis was 6 per cent. Only 5.8 per cent of these women gave any history of a primary or a secondary lesion.

Among more than 500 infants born of syphilitic mothers, Soule found only two infants with undoubted syphilis, after they had had a *negative cord blood reaction at birth.* This result is due to the fact that practically all of our syphilitic patients are closely supervised for the greater part of pregnancy and receive some treatment.

DR. KARL M. WILSON, Rochester, N. Y.—My material is quite different evidently from that of Dr. McCord and Dr. Royston, since we see very little acute syphilis in my clinic. As a matter of fact, in the fourteen years since the clinic

opened, we have had exactly two stillbirths due to syphilis. I attribute this to the extraordinarily efficient manner in which the local Health Board and the profession handle the local venereal problem.

A great many of our syphilitic women go to term. Many of them give birth to living, full-term children and in that type of infant it becomes necessary to use every possible means either to establish a diagnosis of syphilis or to exclude it. I find the radiographic method very valuable, but I have seen pictures of more syphilitic bones this morning than I have in the last fourteen years.

Practically always the cord Wassermann corresponds to the maternal Wassermann. A 4-plus cord Wassermann will be found in the infant born to the mother who shows a 4-plus Wassermann. If the baby does not have syphilis, the positive Wassermann will become negative in the course of some weeks, whereas if it is a congenital syphilitic, the Wassermann will remain positive.

A STUDY OF INTRAUTERINE OXYGEN EXCHANGE*

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(From the Departments of Obstetrics and Gynecology and of Pediatrics, University of Michigan)

OBSTETRIC analgesia and anesthesia has been a controversial subject for many years. While it is generally agreed that some control of pain is desirable, some have attempted to carry this to the point of complete relief. Studies made on patients so relieved have pointed toward both immediate and remote detrimental effects on the fetus.

Schreiber,[1] in 1940, suggested that the use of analgesics and anesthetics in obstetrics may sufficiently alter the maternal blood gases to cause marked decrease in fetal blood oxygen with resultant brain injury due to cerebral anoxia in utero. He points out that if the anoxia persists for even a short period of time the tissue changes may be irreparable and that while the child may survive it is likely to develop neurologic changes later in life. While he admits that other factors must be considered in the production of such anoxia, he places particular emphasis upon the role of analgesic and anesthetic agents used in obstetrics.

Reported studies on maternal and fetal blood gases have revealed certain important data.

Eastman[2] showed that the arterial blood going to the fetus in utero was approximately 50 per cent saturated with oxygen at birth while the maternal arterial blood was usually 95 per cent saturated (Fig. 1). He concluded that: "The very high unsaturation of fetal blood in respect to oxygen indicates that the full-term fetus in utero exists normally in a state of cyanosis," and also "Viewed by adult standards the blood reaching fetal tissues is low in oxygen but for needs of the fetal organism it is evidently adequate." He also suggested that the high oxygen capacity, or hemoglobin content of fetal blood is an adaptive or acclimatization phenomenon due to the low oxygen tension to which the fetal blood in the capillaries is subjected, a tension that is estimated at less than 40 mm. of mercury. Steele and Windler[3] reported similar findings in blood studies on animals and demonstrated that the fetal blood gases fluctuated markedly with muscular work on the part of the mother and that uterine contractions and relaxation sometimes markedly reduced the blood oxygen content.

Recently Smith[4] pointed out that with certain anesthetic agents, notably nitrous oxide, the maternal and fetal blood oxygen levels were reduced, and suggested possible fetal injury because of it. Study of his report, however, reveals that, although the oxygen levels were lower

*Read, by invitation, at the Sixty-Sixth Annual Meeting of the American Gynecological Society, Colorado Springs, Colo., May 26 to 28, 1941.

when nitrous oxide was used, there were actually fewer apneic or asphyxiated babies in the group receiving nitrous oxide than in the group receiving ether. Only two babies out of twenty failed to breathe immediately when nitrous oxide was used as compared with 7 out of 21 when ether was used in comparable types of delivery. This would suggest that the oxygen tension in the blood might not bear the significant relationship to asphyxia that we have supposed.

In view of the existing controversy and the many different opinions, we also undertook a study of the problem. Our purpose was to determine in rabbits, the effect of various analgesic and anesthetic agents on the maternal blood oxygen and carbon dioxide content, the fetal blood oxygen and carbon dioxide content in utero and finally to study microscopically the brains of fetuses delivered from animals subjected to these agents. This report details our experiences with sodium pentobarbital and nitrous oxide.

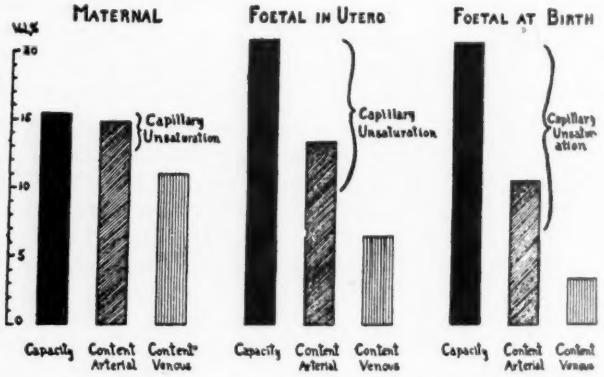

Fig. 1.—Chart showing oxygen relationships of maternal and fetal bloods.

METHODS

For the microscopic study of the fetal brains, the pregnant rabbits were given the sodium pentobarbital or nitrous oxide during the last few days of their pregnancy. The time of administration of the anesthetic agent prior to delivery varied from one to ten days. Early in the study we found that if the anesthesia was given too near to the time of delivery the animal would not care for her young.

Sodium pentobarbital was given to the rabbits intravenously. The initial dose was from 0.1 to 0.3 Gm. (1.5 to 4.5 gr.). In some rabbits, this dose was repeated one to three times in order to maintain a constant deep surgical anesthesia for from one to six hours. Our rabbits varied in weight from 8 to 11 pounds, and this dose when compared with clinical doses used in obstetrics would appear very large. For purposes of this study, however, it was felt that such intense dosage was desirable. The animals were allowed to deliver at term. One fetus was killed at birth and the brain carefully removed intact, examined grossly, and prepared for section. Thereafter one fetus was killed each week and the brains studied in a similar manner in order to determine whether any changes had taken place. The brains from

several fetuses removed at the time of cesarean section under sodium pentobarbital were also studied.

In using nitrous oxide the gas was administered to pregnant rabbits approximately the same interval before term as in the sodium pentobarbital experiment. The anesthetic was administered by an experienced anesthetist by a semi-open flow system with a rebreather in the circuit. A small tight-fitting mask was used. A mixture of 90 per cent nitrous oxide and 10 per cent oxygen was given for one-half hour. The animals were allowed to deliver and the brains of fetuses were studied in a manner similar to that described for the sodium pentobarbital-treated animals.

The brains were carefully studied both grossly and microscopically by Dr. Konstantin Sharenberg, Assistant Professor and Pathologist at the Neuropsychiatric Institute of the University of Michigan. To date 58 brains have been examined (Table I). In none could any evidence of gross or cytologic abnormality be seen. The control brains were identical in all respects with those delivered from the anesthetized animals. The changes usually ascribed to cerebral anoxia consist of focal necrosis with loss of cellular outline and nuclear structure but no changes even remotely suggesting these changes were observed.

TABLE I. FETAL BRAINS EXAMINED GROSSLY AND BY MICROSCOPIC SECTION

SODIUM PENTOBARBITAL ANESTHESIA		N_2O 90% + O_2 10% ANESTHESIA		CONTROLS	
At birth	12	At birth	11	At birth	3
At 1 week	5	At 1 week	6	At 1 week	2
At 2 weeks	4	At 2 weeks	5	At 2 weeks	2
At 3 weeks	2	At 3 weeks	2	At 3 weeks	1
At 4 weeks	0	At 4 weeks	1	At 4 weeks	1
At 5 weeks	0	At 5 weeks	1	At 5 weeks	0
Total	23		26		9

While it was not possible to attempt behavior studies on the rabbits, it may be said that these animals exhibited normal habits and growth rates when compared with others in the laboratory. In addition, we are privileged to report on an unpublished work carried out in the Department of Psychology by Mr. Stewart Armitage, in which rats born of mothers to whom sodium pentobarbital was given during the latter part of their pregnancies were tested for intelligence by the maze technique established by Dr. Norman Maier. It has been found that these animals showed an ability to solve the maze equal to that of the normal controls.

The study of the maternal and fetal blood gases was carried out as follows:

Under local anesthesia the uterus was exposed through a small incision at or within a few days of term. Maternal and fetal blood samples were obtained under oil within a few minutes of each other. In order to avoid disturbing placental circulation or fetal environment, one fetus was brought under the opening in the abdominal wall, and, without opening the uterus, a needle was inserted through the uterus into the fontanel of the fetus. In this manner, we were usually able

TABLE II. PRENATAL ANESTHESIA WITH SODIUM PENTOBARBITAL

NO.	DATE OF TERM	DAYS BEFORE TERM	DURATION OF ANESTHESIA	DOSE 1 GR. PER C.C.	MATERNAL VENOUS BLOOD				FETAL SAGITTAL SINUS BLOOD			
					OXYGEN		CARBON DIOXIDE		OXYGEN		CARBON DIOXIDE	
					BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER
2	10/11	4	0	0	10.5	56.5	56.5		0.9	0.3	69.7	67.1
	1/ 5	1	1 hr.	1.5	15.1	12.8	52.6	48.6	1.8	0.8	54.1	60.9
					14.6		50.5		2.4		55.7	
1	10/10	5	3 hr.	3.0								
		4	2 hr.	2.0	8.5	7.6	44.3	51.0				
	11/24	4	1 hr.	1.5	13.7	13.4	49.1	54.1				
					8.6		52.9				45.5	51.2
		1	1½ hr.	1.5		10.5		42.9		2.7		40.3
5	12/11	8	1¼ hr.	1.5								
	1/12	2	1 hr.	1.5	11.4	11.1	55.0	58.6	3.6	1.2	44.8	60.8
						12.3		57.3				
7	11/ 1	1	1¼ hr.	1.5								
4	10/20	5	3½ hr.	4.75								
		3	2¾ hr.	2.0	15.6	11.5	32.7	40.6				
8	10/31	9	1 hr.	1.5	13.3	12.6	35.0	56.8				
		3	5¾ hr.	2.5								
12	11/15	10	1½ hr.	2.5	14.3	6.9	33.6	54.4				
					11.6		51.1					
14	11/17	3	2½ hr.	3.0								
18	12/ 4	6	1½ hr.	2.5	19.2	8.9	43.4	46.4				
					20.8		52.1					
		1	2½ hr.	2.7					2.6	1.7	56.0	52.6
		0	1 hr.	1.5	10.6		28.6					50.6
16	11/26	7	2 hr.	2.5	10.4	10.5	49.0	49.4				
					11.3		46.0					
20	12/15	0	1 hr.	1.5	9.9	10.8	42.1	42.0		1.8	62.0	65.8
						8.7	52.2			0.3		61.6
										0.3		68.2
9	11/ 1	7	5½ hr.	3.0	15.1	14.6	31.8	38.0	0.3	1.2	74.4	82.1
						8.2		39.0	0.6	0.2	78.6	77.9
	1/ 6	2	1½ hr.	1.5	10.0	5.3	52.8			0.3		77.3
10	11/ 1	8	1 hr.	2.2	14.3		39.4					
15	12/17	2	1 hr.	1.5	8.1	9.0	55.5		0.45	0.3	76.5	58.3
					8.0		58.2	56.7	0.15		74.3	59.7
Average					12.5	10.3	45.9	49.2	1.4	0.8	62.8	62.3
Standard deviation					3.3	2.3	8.8	6.7	1.1	0.6	11.7	9.6

TABLE III. PRENATAL ANESTHESIA WITH N_2O 90% & O_2 10% FOR ONE-HALF HOUR

NO.	DATE OF TERM	DAYS BEFORE TERM	MATERNAL								FETAL SAGITTAL SINUS BLOOD			
			OXYGEN				CARBON DIOXIDE				OXYGEN		CARBON DIOXIDE	
			ARTERIAL		VENOUS		ARTERIAL		VENOUS					
			BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER
2	2/16	1	5.0*	7.4	1.5		47.1*	31.8	61.5*		0.2	0.5	54.9	45.3
19	2/20	3			8.1	11.4			28.3	27.0				
23	2/28	4	8.3	9.9	10.8		41.9	33.5	35.8					
25	3/11	10	16.2	13.4	13.2	10.4	31.4	28.5	33.9	28.6				
8	3/28	10	12.4	12.2	12.9	12.2	44.4	44.0	49.0	43.4				
30	4/ 1	5	12.3	14.7	11.4	13.1	43.8	37.1	42.6	37.4				
9	4/ 6	1	5.7	8.1	12.6 14.4*	2.7*	49.0	34.9	47.4 47.4*	40.5*	0.6	1.0	62.7	46.9
22	4/30	1		5.3	4.9*	2.4*		30.6	40.3*	32.6*	0.4	0.3	52.9	43.0
36	4/21	5	3.3		3.0*	6.3*	30.8		33.7*	42.6*	0.2	0.4	44.7	45.5
37	4/19	1	11.1	8.3*	0.7*	4.7*	34.9	38.6*	51.3	46.0*	0.1	0.0	54.5	61.4
38	4/23	1	12.3	11.9	4.2 15.2	9.0	41.6	38.6	49.1* 40.6	35.7	0.2	0.9	61.4	45.8
41	5/ 2	1	15.4	11.4	7.6*		35.4	28.5	38.3*		0.3	0.0	47.7	36.2
23	5/ 5	1	11.9	8.8	11.6	7.6	26.7	24.3	29.1	29.2	0.2	0.4	60.5	35.1
Average			10.4	10.1	8.8	8.9	38.8	33.7	41.9	36.3	0.3	0.4	54.9	44.9
Standard deviation			4.0	2.8	4.8	3.8	7.04	5.4	8.8	6.8	0.15	0.34	6.03	2.44

*Blood taken from uterine vessel.

to obtain from 0.4 to 0.8 c.c. of blood from each fetus. In some it was obvious that the specimen contained spinal fluid or brain tissue, and these were discarded. All satisfactory specimens were analyzed by Van Slyke-Neill[5] technique. It was impossible to obtain a specimen of arterial blood from the fetuses.

Most of the maternal specimens were obtained from the ear. In some animals arterial specimens could not be obtained. In others venous blood was obtained from the uterine vein, and in these it was discovered that the O_2 and CO_2 content was essentially the same as the findings recorded for blood obtained from the ear. One specimen was obtained from the mother and from one fetus before the anesthetic agent was given. The dose of sodium pentobarbital was the same as used for studies on brain damage, namely 0.1 to 0.3 Gm. After one-half hour blood samples were again obtained. When nitrous oxide was used specimens were obtained for control and then the gas was given in the concentration of 90 per cent to 10 per cent oxygen for one-half hour following which fresh blood samples were obtained and analyzed. In the specimens from the rabbits receiving nitrous oxide, the gas was corrected for by the method of Orcutt and Waters.[6]

RESULTS

The results of these blood studies are shown in Tables II and III. It will be noted that the results show considerable variation in different animals and in the same animals at different times. Similar variation was noted by Eastman (Table IV) and is probably accounted for on the basis of factors previously mentioned; namely, uterine contractions, maternal activity, etc. The fetal blood specimens are obviously venous in origin and while the O_2 content is somewhat lower the results are, in general, comparable to the readings obtained by Eastman and Smith in the human being. In neither mother nor fetus do our results reveal any significant alteration in blood O_2 as a result of sodium pentobarbital or nitrous oxide administration.

TABLE IV. SHOWING THE OXYGEN RELATIONSHIPS OF MATERNAL AND FETAL BLOOD AT BIRTH EXPRESSED IN VOLUMES PER CENT

CASE	MATERNAL				FETAL			
	CAP.	CONT. ART.	CONT. VEN.	CAP. UNSAT.	CAP.	CONT. ART.	CONT. VEN.	CAP. UNSAT.
1	14.5	13.8	10.0	2.6	20.2	9.8	2.4	14.1
2	13.8	13.1	10.1	2.2	22.4	12.3	5.9	13.3
3	17.1	16.2	12.8	2.6	18.8	9.5	1.4	13.3
4	14.8	14.1	9.9	2.8	20.5	10.2	3.3	13.8
5	15.6	14.8	10.2	3.1	22.5	12.7	6.0	13.1
6	16.3	15.5	11.0	2.9	21.0	8.2	1.3	16.3
7	17.0	16.2	12.8	2.5	20.9	8.8	2.7	15.1
8	16.0	15.2	12.9	2.0	19.5	11.2	5.3	11.2
9	15.2	14.4	10.5	2.8	19.8	9.9	2.3	13.7
10	12.4	11.8	9.0	2.0	22.3	12.2	5.4	13.5
11	15.4	14.6	10.0	3.1	20.8	9.3	1.5	15.4
12	15.5	14.7	10.5	2.9	22.5	13.2	5.7	13.0
13	16.1	15.3	11.0	3.0	19.9	10.4	2.0	13.7
14	14.9	14.2	10.6	2.5	20.3	10.1	2.9	13.8
15	16.6	15.8	13.3	2.0	20.8	9.8	1.9	14.9
Average	15.4	14.7	11.0	2.6	20.8	10.5	3.3	13.9

DISCUSSION

The combined results of this study would seem to indicate that the likelihood of intrauterine cerebral anoxia with resulting cerebral damage in fetuses whose mothers are subjected to either sodium pentobarbital or nitrous oxide is remote. The fact that the pregnant animals were subjected to concentrations of both agents far in excess of the dose used clinically and yet gave birth to apparently normal fetuses whose brains showed no demonstrable injury points to the fact that no ill effects are suffered by the rabbit fetus in utero.

While we do not feel that these findings remove all criticism from the use of these agents, we are of the opinion that they tend to disprove the claims of Schreiber that they may be the frequent cause of serious cerebral damage to the fetus in utero. It is true that the results of this study in rabbits cannot be said to apply directly to the use of these agents in the human being, because of species differences, but it seems reasonable to assume that if they could cause damage certainly such intense doses would have produced some demonstrable evidence.

The fact that this study as well as others in the literature indicate that the fetal blood oxygen is normally much lower than that required for the adult, suggests that the fetal tissues are capable of using the available oxygen more efficiently or that the rapid rate of the fetal heart may result in an increased minute volume flow of blood which could satisfy the oxygen needs of the fetal tissues. This would account for the extremely low readings obtained in the specimens from the superior longitudinal sinus. It would also suggest that moderate variations in the maternal blood oxygen would be of less importance to the fetus than has been previously supposed. It would seem therefore that if any criticism of the use of these agents is justifiable it must be on some other basis than that they produce anoxia in utero with resultant cerebral damage.

This study suggests that since no significant changes were observed following such large doses of sodium pentobarbital and high concentrations of nitrous oxide that the clinical use of these agents in reasonable amounts would be unlikely to cause harm to the human fetus. Just what constitutes reasonable amounts of these drugs may be debatable, but it is our opinion that 0.1 to 0.3 Gm. of sodium pentobarbital may be safely used as an analgesic drug in obstetrics. While it has been demonstrated that nitrous oxide in the concentration of 90 per cent with 10 per cent oxygen can produce significant alterations of the blood gases in the adult, we feel that concentrations up to 75 per cent N_2O and 25 per cent O_2 can be used without danger to either the mother or fetus.

We wish to express our appreciation to Miss Kathleen Sturgeon for her invaluable assistance in the administration of the anesthetics to the animals.

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DISCUSSION

DR. WILLIAM J. DIECKMANN, CHICAGO, ILL.—Dr. Kretzschmar and his co-workers have carried out a very carefully planned experiment which is timely. As he mentioned, several men have attributed various degrees of fetal pathology to the use of barbiturates in the mother. Medicolegal complications have arisen in several localities. Dr. Kretzschmar has shown that in the rabbit many times the therapeutic dose of nembutal has no effect on the blood gases of the mother or fetus. Furthermore, they could demonstrate no damage to the brain.

Dr. Kretzschmar mentioned that animal experimentation cannot be compared with human beings. Barcroft has shown that the fetal hemoglobin of the rabbit, sheep, and goat takes up oxygen more readily than the human fetal hemoglobin does. He has also shown that there is a very exact regulation of the blood flow in the mother and fetus of these animals. The fetus lives in a very low percentage of oxygen but, so far as I know, no one has determined just how little oxygen the fetus actually needs. It is well protected and its movements are limited. These conditions probably account for the very low oxygen saturation in the fetal blood.

Another difference between the human being and the animal is in the type of placentation. Man and the higher apes are the only ones that have a hemochoreal type of placenta, which permits easy and quick division of blood gases in both directions. I believe many of these studies on fetal respiration and the effect of drugs must be started on the human being. It is feasible during a cesarean section under local anesthesia to deliver the cord through a small incision in the uterus and obtain specimens of blood.

DR. FRED L. ADAIR, CHICAGO, ILL.—The oxygenation of the fetus does not depend upon the respiratory movements of the fetus but on its cardiac circulation. In other words, drugs might have an effect on the fetal respiratory apparatus which would not be quite comparable to what takes place in the newborn infant when the respiratory center is all important. One point I would like to have Dr. Kretzschmar discuss in his closing remarks is what effects, if any, were observed in the rabbits after they were delivered so far as the establishment of their respiration was concerned. I think this is particularly important, because the anoxemia which is quite prolonged sometimes does considerable harm to the newborn baby.

Another point is worthy of discussion: I understand that in these experiments the gases and anesthetics were given during pregnancy and not during labor. Of course, we give these agencies during labor in the human being, and it is not only the direct effect of these agencies on the fetus but on the course of labor and the uterine contraction that is important. I think we should understand that the uterine contractions have a very important function to perform in maintaining circulation in the uterine sinuses and, of course, anything that interferes with that will affect the fetus and alter its condition.

Dr. F. F. Snyder has been doing some very careful work on fetal respiratory movements in the rabbit. From his experiments it is quite obvious that the rabbit does have respiratory movements in utero, which, of course, have nothing to do with its oxygenation.

We do encounter definite changes in the fetus due to acute anoxemia. We see these changes resulting from the sudden death of the fetus, where there are petechial hemorrhages scattered throughout the viscera. The most classical example is where there is complete separation of the placenta which results in death of the fetus from acute anoxemia with numerous visceral petechial hemorrhages, and as a result there are changes in the brain. It is only reasonable to expect that there would not be such striking evidence of these changes, particularly in the brain, in the more slowly developing cases of anoxemia from analgesia. The knowledge that we do get them would lead us to anticipate changes in the brain cells which would not be discernible even under microscopic examination. This is an extremely complicated problem. It seems very difficult to get general agreement on such a fundamental fact as to whether or not the fetus has respiratory movements in utero. It is more difficult therefore to interpret some of these less concrete evidences of fetal respiration and circulation.

DR. FRANCIS C. GOLDSBOROUGH, BUFFALO, N. Y.—I do not think that we should carry the results of these experiments over to clinical practice, because in these experiments animals were given sedatives during pregnancy, the effect of which was entirely worn off when they were delivered. That is very different from giving sedatives to patients in whom the effect is still present when the child is delivered, so that it does not breathe properly and injuries to the child result.

DR. KRETZSCHMAR (closing).—I did not wish to create the impression that this study removes all of the criticism from the use of these analgesic and anesthetic agents. The study was undertaken to find out whether these drugs were capable of producing a sufficient decrease of oxygen level. If a depression of the fetus occurs sufficient to produce an apnea, then it is certainly conceivable that an anoxemia may develop. Conditions comparable to an acute anoxemia in the fetus in utero would probably be preceded by a serious condition in the maternal organism.

Some of the animals which were delivered at the time of section were perfectly normal and breathed readily. The administration of these substances did stop all evidence of intrauterine respiratory activity. I do not think we can eliminate the possibility that certain individuals are sensitive to or show toxic manifestations from these agents, but I do believe that the study tends to disprove that cerebral damage can be produced in utero by the administration of these agents to the mother during pregnancy or early in labor.

A CONSIDERATION OF THE CAUSE AND POSSIBLE LATE EFFECT OF ANOXIA IN THE NEWBORN INFANT*

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IT HAS been pointed out by Schreiber[10, 11] that serious neurologic manifestations in children are frequently associated with neonatal apnea. He postulates fixed degenerative brain lesions in the newborn as the result of "paranatal anoxia." If such a relationship exists, the responsibility of the obstetrician cannot be minimized.

The purpose of this study was first, to analyze the factors responsible for delayed respirations; and second, to determine the relationship between neonatal apnea and later mental development, providing methods were employed to administer oxygen during the apneic period. As anoxia may develop at any time during pregnancy and delivery, it is not possible to prevent all anoxic damage. Apnea, however, exists when the organism fails to breathe. In the absence of normal respirations, the newborn will become rapidly anoxic, unless oxygen is supplied. Oxygen may be supplied by administering oxygen to the mother as long as the cord pulsates. When pulsations cease, oxygen may be administered directly, if artificial respiration is maintained in the presence of oxygen.

I. A CONSIDERATION OF THE VARIOUS OBSTETRIC FACTORS IN THE PRODUCTION OF DELAYED RESPIRATION IN THE NEWBORN INFANT

Material and Methods.—The records from 1,097 consecutive deliveries were studied. Ninety-two of these records were omitted. The omissions are tabulated in Table I. Seventy-three records had insufficient data. Babies weighing less than 1,000 Gm. were considered previable. As only 5 cesarean sections were performed in this series, they were omitted. The purpose of the study required the omission of babies having no heart tones at the onset of labor. One hydrocephalic baby delivered following a craniotomy.

TABLE I. TABULATION OF OMITTED CASES

OMISSIONS	CASES	BABIES STILLBORN OR DIED
Insufficient data	73	2
Cesarean section	5	1
Previable (under 1,000 Gm.)	6	6
Stillborn, no heart tones at onset of labor	7	7
Congenital anomaly (craniotomy)	1	1
Total	92	17
Total number of babies		1,097

Analgesia.—Only one technique is used for all patients receiving analgesia. During the antenatal period an effort is made to prepare

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each patient for labor. She is told to expect some pain but that "relief consistent with safety" to the baby will be given. As pains become hard, each patient receiving analgesia is given 3 gr. of pentobarbital sodium and 1/200 of a gr. of scopolamine. After forty-five minutes, 1/400 of a gr. of scopolamine is given, and the latter is repeated as often as necessary thereafter but not more often than every two hours. This dosage is smaller than that frequently employed, and, of course, the percentage of satisfactory amnesia is also lower. No attempt has been made to obtain complete amnesia. Extreme restlessness is unusual following this regime.

With bulging in primiparas or complete dilatation in multiparas, 50 per cent nitrous oxide and oxygen is given with each pain, and expulsive efforts are encouraged. In all primiparas and in multiparas with strong perineal bodies, local infiltration anesthesia is employed as crowning occurs. At the proper time a *deep* episiotomy permits the head to deliver with very little resistance. When necessary, low or midforceps may be applied and traction used during the pains with no general anesthesia. Following this regime, anesthesia is a minimal factor in the production of "paranatal anoxia." Neither pituitrin nor ergonovine is given to hasten separation of the placenta.

Oxygen.—Immediately following the birth of the head, the 50 per cent nitrous oxide-oxygen mixture is discontinued and oxygen is given. The mother breathes oxygen until the cord stops pulsating. In many cases only oxygen is given because nitrous oxide is omitted if the analgesia is satisfactory.

Newborn Care.—The baby is placed on the mother's abdomen immediately following birth, covered to preserve warmth and left undisturbed until pulsations in the cord cease. Mucus is removed by means of a soft rubber ear syringe. The time interval between birth, the first regular breathing, and the first vigorous cry is recorded in all cases. We have classified the respiratory response as, *no apnea, mild apnea, severe apnea,* and *stillborn. No apnea* is said to exist, if at birth the color is good or improves quickly and if the baby breathes regularly in less than thirty seconds. The baby is not considered apneic if breathing is regular and the color good, even though the cry is delayed. *Mild apnea* indicates a slightly delayed response, respirations being delayed more than thirty seconds but well established in one minute or less. In this type cyanosis clears promptly as breathing becomes regular. *Severe apnea* is said to be present if both breathing and crying are delayed more than one minute. An attempt is made to supply oxygen to these babies through the cord until pulsations cease or until signs of placental separation are present. Then if spontaneous respirations have not occurred, gentle artificial respiration in the presence of oxygen or oxygen and CO_2 is started. As every effort is made to prevent anoxia in all apneic babies, we do not wait for long intervals to see if resuscitation is necessary. Once respirations are established, oxygen and CO_2, if employed, is discontinued and oxygen is given until the color remains pink. During resuscitation the baby is kept warm either in a crib or in a warm bath and the air passages are kept clear. All babies developing cyanosis

in the first few days of life are considered to be severely apneic. *Neonatal death* indicates an infant death occurring within twelve days of birth or before discharge from the hospital. These deaths are included as some may reflect the remote effect of cellular anoxia.

The incidence of apnea, stillbirth, and neonatal death for the cases omitted and for the cases to be analyzed is tabulated in Table II. The

TABLE II. INCIDENCE OF NEONATAL APNEA AND FETAL DEATH IN CASES OMITTED AND IN ENTIRE SERIES

	CASES	PER CENT				
		NO APNEA	MILD APNEA	SEVERE APNEA	STILL-BORN	DIED
Entire series	1,097	82.3	8.7	5.8	1.8	1.4
Omitted	92	70.7	6.4	4.4	14.1	4.4
Series to be used	1,005	83.3	8.9	6.0	0.7	1.1

gross fetal mortality, 3.2 per cent for the entire series, is uncorrected and includes all previable babies. One and eight-tenths per cent of all babies were stillborn. The high incidence of stillbirths and neonatal deaths in the omitted group is explained by the fact that all previable babies and those with no heart tones at the onset of labor are included.

DATA

Length of Labor.—The incidence of neonatal apnea and fetal death in relation to the duration of labor is presented in Table III. It is fre-

TABLE III. INCIDENCE OF NEONATAL APNEA AND FETAL DEATH IN RELATION TO DURATION OF LABOR

DURATION OF LABOR	CASES	PER CENT				
		NO APNEA	MILD APNEA	SEVERE APNEA	STILL-BORN	DIED
0- 4 hours	31	80.6	6.5	12.9	0	0
5-11 hours	182	81.3	6.5	10.4	0.6	1.2
12-18 hours	80	85.0	7.5	6.3	0	1.2
18 plus hours	40	87.5	12.5	0	0	0
Average, all normal primiparas	333	82.9	7.5	8.4	0.3	0.9

quently stated that a long labor is detrimental to the baby. To eliminate conflicting factors only normal primiparous labors are considered. If during a long labor the mother receives ample rest, nourishment, and fluids and if operative procedures are avoided, long labor does not seem to be harmful to the baby. In the short and precipitate labors, there is a marked increase in the percentage of severely apneic babies.

Duration of Second Stage.—The incidence of neonatal apnea and fetal death in relation to the duration of the second stage and to outlet forceps deliveries, in otherwise normal primiparas, is shown in Table IV. Only normal primiparous deliveries have been considered, as multiparas cannot be said to have a true second stage. If abnormal labors had been included, the factor of unusual trauma would distort the figures. Very little difference is noted in the incidence of apnea, whether the second

TABLE IV. INCIDENCE OF NEONATAL APNEA AND FETAL DEATH IN RELATION TO DURATION OF SECOND STAGE AND TO OUTLET FORCEPS DELIVERIES IN OTHERWISE NORMAL PRIMIPARAS

DURATION OF SECOND STAGE	CASES	PER CENT				
		NO APNEA	MILD APNEA	SEVERE APNEA	STILL-BORN	DIED
0-1 hour	212	84.4	5.2	9.4	0.5	0.5
1-2 hours	82	81.7	11.0	7.3	0	0
Over 2 hours	39	77.0	12.8	5.1	0	5.1
Average, normal primiparas	333	82.9	7.5	8.4	0.3	0.9
Outlet forceps	76	75.0	13.2	10.5	0	1.3

stage lasts one or two hours or if it is less than one hour in duration. When the second stage lasts longer than two hours, there is definite evidence of fetal injury.

The figures for simple outlet forceps have been included, as this type of delivery is frequently chosen in the belief that the procedure prevents trauma to the baby's head. The incidence of apnea is high when outlet forceps have been used. Cole and associates[1] noted, "Asphyxia occurs with considerably greater frequency in low forceps delivery than in spontaneous delivery. However, in most of these cases episiotomy is also performed, which necessitates anesthesia." In our group no general anesthesia was given, as local anesthesia makes the use of outlet forceps almost painless after a *deep* episiotomy is performed. The incidence of apnea is higher when outlet forceps are used than when the second stage is two hours or less in duration. The evidence indicates that unless the second stage is unduly prolonged, the practice of purely conservative obstetrics produces fewer apneic babies.

Rupture of Membranes.—The incidence of neonatal apnea and fetal death in relation to the time of rupture of membranes is shown in Table V. Only normal primiparous deliveries are included in this group. Ab-

TABLE V. INCIDENCE OF NEONATAL APNEA AND FETAL DEATH IN RELATION TO TIME OF RUPTURE OF MEMBRANES

MEMBRANES RUPTURED	CASES	PER CENT				
		NO APNEA	MILD APNEA	SEVERE APNEA	STILL-BORN	DIED
Early	94	73.4	8.5	16.0	0	2.1
Late	221	86.3	6.8	5.9	0.5	0.5
Not noted	18	88.8	11.2	0	0	0
Average, all normal primiparas	333	82.9	7.5	8.4	0.3	0.9

normal deliveries are omitted as the resultant trauma would influence the percentage of apneic babies. Normal multiparas are omitted as their inclusion would minimize the importance of trauma incident to the dilatation of a nulliparous birth canal. It would seem that the membranes serve a protective purpose as there is a marked increase in mild and severe apnea and neonatal death when the membranes are ruptured early in labor. The membranes are said to have been ruptured early if the rupture occurred prior to the onset of labor or early in the first stage.

Abnormal Deliveries.—The incidence of neonatal apnea and fetal death in relation to normal and abnormal deliveries is shown in Table VI. Trauma plays an important role in the production of apneic babies.

TABLE VI. INCIDENCE OF NEONATAL APNEA AND FETAL DEATH IN RELATION TO NORMAL AND ABNORMAL DELIVERIES

TYPE OF DELIVERY	CASES	PER CENT				
		NO APNEA	MILD APNEA	SEVERE APNEA	STILL-BORN	DIED
All normal cases	815	87.5	6.9	4.8	0.2	0.6
All abnormal cases	190	65.8	17.4	11.0	2.1	3.7
Average all cases	1,005	83.3	8.9	6.0	0.7	1.1

All abnormal deliveries are included in one group, since the trauma in abnormal deliveries is of the same type, varying only in degree. Whether delivery is accomplished by the use of outlet or midforceps, or by version or breech extraction, the head is delivered through the pelvis with more sudden compression than is found in normal deliveries. There is a marked increase in mild apnea, severe apnea, stillbirths, and neonatal deaths following abnormal deliveries, with a possibility of serious anoxia prior to delivery.

Parity.—The incidence of neonatal apnea and fetal death in relation to parity is shown in Table VII. When analgesia is not used the per-

TABLE VII. INCIDENCE OF NEONATAL APNEA AND FETAL DEATH IN RELATION TO PARITY

PARITY	CASES	PER CENT				
		NO APNEA	MILD APNEA	SEVERE APNEA	STILL-BORN	DIED
Normal multiparas (no analgesia)	264	91.2	5.7	1.9	0.4	0.8
Normal primiparas (no analgesia)	65	89.3	7.7	1.5	0	1.5
All multiparas	554	86.6	8.3	3.1	0.7	1.3
All primiparas	451	79.4	9.5	9.5	0.7	0.9

centage of nonapneic babies is about the same in primiparas as in multiparas. However, when all multiparas are compared with all primiparas, there is a marked decrease in the percentage of nonapneic babies in the primiparous group. An important contributing factor, to the increased percentage of apneic babies in the "all primiparous group," is the inclusion of those babies delivered by outlet forceps.

Maternal Anemia.—The incidence of neonatal apnea and fetal death in relation to maternal anemia is shown in Table VIII. As parity did

TABLE VIII. INCIDENCE OF NEONATAL APNEA AND FETAL DEATH IN RELATION TO MATERNAL ANEMIA

MATERNAL HEMOGLOBIN	CASES	PER CENT				
		NO APNEA	MILD APNEA	SEVERE APNEA	STILL-BORN	DIED
Under 11.0 Gm.	20	75.0	10.0	10.0	5.0	0
11-12.9 Gm.	232	86.2	9.9	3.0	0	0.9
13-14.9 Gm.	465	88.0	5.4	6.0	0.4	0.2
15 Gm. and over	98	90.9	6.1	2.0	0	1.0
Average all normal primiparas and multiparas	815	87.5	6.9	4.8	0.2	0.6

not greatly alter the incidence of apnea in normal deliveries, both multiparas and primiparas are included in this analysis. Except in cases of post-partum hemorrhage, the hemoglobin reading was taken on the fourth post-partum day. It will be noted that each group presenting a better average hemoglobin had a lower incidence of apnea. The same trend is shown when this group is separated into those having analgesia and those without analgesia. However, in the patients having a severe degree of anemia, if analgesia is given, the incidence of severe apnea is increased.

Analgesia.—The incidence of neonatal apnea and fetal death in relation to analgesia is shown in Table IX. A definite increase in severe

TABLE IX. INCIDENCE OF NEONATAL APNEA AND FETAL DEATH IN RELATION TO ANALGESIA

	CASES	PER CENT				
		NO APNEA	MILD APNEA	SEVERE APNEA	STILL-BORN	DIED
All analgesia	486	85.2	7.4	6.8	0.2	0.4
No analgesia	329	90.9	6.1	1.8	0.3	0.9
Average all normal primiparas and multiparas	815	87.5	6.9	4.8	0.2	0.6

apnea is noted in the analgesia group. The higher infant mortality in the "no analgesia group" can be explained by the fact that analgesia was withheld in patients having ante-partum hemorrhage or showing signs of toxemia when fetal heart tones were present.

The relation of parity and normal and abnormal delivery to the degree of analgesia is shown in Table X. Less than 50 per cent had

TABLE X. THE RELATION OF PARITY, NORMAL AND ABNORMAL DELIVERY TO DEGREE OF ANALGESIA

TYPE OF DELIVERY	CASES	DEGREE OF ANALGESIA		
		GOOD AMNESIA	AMNESIA BUT EXCITEMENT	POOR AMNESIA
Normal multiparas	218	13.7	8.3	78.0
Abnormal multiparas	32	15.6	18.7	65.7
Normal primiparas	268	42.2	20.9	36.9
Abnormal primiparas	109	67.0	5.5	27.5
Average all cases	627	41.4	8.1	50.5

satisfactory amnesia. This very low figure is undoubtedly due to the small amount of analgesic drug used. Eight and one-tenth per cent of all patients receiving analgesia exhibited some degree of excitement.

The incidence of neonatal apnea and fetal death in relation to the degree of analgesia is shown in Table XI. Only normal primiparous labors are considered, as other factors alter the relationship if the entire group is analyzed. If birth occurs during the excitement stage there is an increase in the percentage of fetal deaths. The high incidence of severe apnea in those receiving poor amnesia may be due to an unusual reaction to the drug used.

The incidence of neonatal apnea in relation to the time interval between birth and the administration of the analgesic drug is shown in

TABLE XI. INCIDENCE OF NEONATAL APNEA AND FETAL DEATH IN RELATION TO DEGREE OF ANALGESIA

DEGREE OF ANALGESIA	CASES	PER CENT				
		NO APNEA	MILD APNEA	SEVERE APNEA	STILL-BORN	DIED
Good amnesia	151	81.3	11.4	6.0	0	1.3
Excitement, good amnesia	21	81.0	4.8	9.4	4.8	0
Poor amnesia	96	81.3	2.1	16.6	0	0
Average all normal primiparas with analgesia	268	81.3	7.5	10.1	0.7	0.4

Table XII. The highest percentage of apneic babies is noted if the time interval is from one to two hours. If the time interval is more than two hours the incidence of apnea decreases.

Prematurity.—The incidence of neonatal apnea and fetal death in relation to prematurity is shown in Table XIII. Our results are similar to those published by others, indicating a great increase in severe apnea and fetal death in prematures when compared with the mature group. As maturity advances, the effects of trauma are less severe, even when abnormal deliveries are considered.

TABLE XII. INCIDENCE OF NEONATAL APNEA IN RELATION TO TIME OF ADMINISTRATION OF ANALGESIC DRUG

INTERVAL BETWEEN ADMINISTRATION OF ANALGESIC DRUG AND DELIVERY	CASES	PER CENT				
		NO APNEA	MILD APNEA	SEVERE APNEA	STILL-BORN	DIED
One hour or less	167	85.0	7.8	6.6	0	0.6
One to two hours	194	83.5	7.2	8.3	0.5	0.5
Two to three hours	66	87.8	7.6	4.6	0	0
Over three hours	59	88.1	6.8	5.1	0	0
Average all normal primiparas and multiparas	486	85.2	7.4	6.8	0.2	0.4

TABLE XIII. INCIDENCE OF NEONATAL APNEA AND FETAL DEATH IN RELATION TO PREMATURITY

WEIGHT OF BABY	CASES	PER CENT				
		NO APNEA	MILD APNEA	SEVERE APNEA	STILL-BORN	DIED
1,000 to 2,500 Gm.	25	72.0	4.0	16.0	0	8.0
2,500 to 4,000 Gm.	718	88.0	6.7	4.6	0.3	0.4
Over 4,000 Gm.	72	87.5	9.7	2.8	0	0
Average all normal primiparas and multiparas	815	87.5	6.9	4.8	0.2	0.6

II. A PRELIMINARY REPORT ON THE RELATIONSHIP BETWEEN DELAYED RESPIRATION AT BIRTH AND LATER MENTAL AND PHYSICAL DEVELOPMENT

The purpose of this portion of the study was to determine the value of supplying oxygen to all babies during the apneic period. As the number of apneic babies in this group is too small to be of statistical significance this discussion is in the nature of a preliminary report. It is

our intention to continue testing the local children each year, as they are admitted to the public school system, until the series is large enough to be of clinical importance.

Material and Methods.—Eight hundred and sixty-one consecutive births were used in this follow-up study. Owing to peculiar local conditions a large number of patients come from distant points. Therefore it was possible to make tests on only 270 children. Of the 861 babies, 29 failed to survive. As all previables were included, the uncorrected fetal mortality was 3.3 per cent. Eight hundred and thirty-two babies were discharged from the hospital alive. The present status of the 832 is shown in Table XIV. A summary of the birth records of the 270 children, now in school, is shown in Table XV.

TABLE XIV. TABULATION OF OMITTED CASES

Children in school and tested	270
Children out of school—not tested (injury, rheumatic fever, etc.)*	9
Died after discharge from the hospital†	8
Nonresidents	378
Moved	155
Unable to trace (moved?)	3
Illegitimate (not known)	9
Total	832

*It is planned to test these children as the study is completed.

†Five died of upper respiratory infections; two were cretins; one died of accidental causes; only one, a premature cretin, was apneic at birth.

TABLE XV. INCIDENCE OF NEONATAL APNEA ON TESTED CHILDREN

	CASES	PER CENT		
		NO APNEA	MILD APNEA	SEVERE APNEA
No analgesia	159	96.2	2.5	1.3
Analgesia	111	74.8	17.1	8.1
Total	270	87.4	8.5	4.1

Two methods of testing the 270 school children were used. First, each child was given the *Kuhlmann-Anderson[7] Intelligence Tests.* These tests were conducted by examiners working under well-trained supervision. The tests were scored by one individual. From this data median and average intelligence quotients were obtained for the entire group, for those having analgesia, for those in whom analgesia was not employed, and for the group that were apneic at birth.

To supplement the Kuhlmann-Anderson[7] tests, the Haggerty-Olson-Wickman[4] behavior rating schedules were used. This evaluation demonstrates both the weaknesses and assets of the individual child. One portion of the tests tends to bring out the frequency of various behavior problems. The balance of the test gives a graphic rating for various intellectual, physical, social, and emotional traits. The schedules were completed in each case by the teacher who was in daily contact with the child. Schedule A in the test consists of a list of behavior problems occurring in elementary school children, and Schedule B consists of a graphic scale for each of the 35 intellectual, physical, social, and emotional traits that go to make up a well-developed child. In each schedule a high score depicts too frequent occurrence of behavior problems or

undesirable deviations from a normal development, and low scores represent a desirable deviation from the typical behavior of a group of children.

DATA

The distribution of intelligence quotients in the entire group of 270 children is shown in the histogram in Fig. 1. The median is 112.4, the average 111.4. In Fig. 2 the distribution of I. Q.'s of 159 children is shown. No analgesia was used in this series. The median I. Q. was 111.7 and the average I. Q. was 110.8. In Fig. 3 the distribution of I. Q.'s of 111 children is shown. Analgesia was used in this group. The median I. Q. was 113.2 and the average I. Q. was 112.3. In Fig. 4 the distribution of I. Q.'s for 34 children who were asphyxiated at birth is shown. The median I. Q. was 110.4, and the average I. Q. was 112.1.

The median scores on the Haggerty-Olson-Wickman rating schedules as well as normative values reported by Haggerty-Olson-Wickman[4] are shown in Table XVI. Separate medians are not reported according to

TABLE XVI. MEDIAN SCORES ON THE HAGGERTY-OLSON-WICKMAN BEHAVIOR RATING SCHEDULES "A" AND "B"

	CASES	MEDIAN SCORE	
		SCHEDULE "A"	SCHEDULE "B"
"No analgesia" group	159	8.9	64.5
"Analgesia" group	111	9.7	63.0
"Asphyxia" group	34	7.0	62.9
Normative value*		8.6	65.4

*From Haggerty, Olson and Wickman.[4]

sex, as the number of cases is, as yet, too small. This series fails to reveal a marked trend, as there is no striking difference between the various groups of cases. The data tend to indicate that behavior problems occur with no greater frequency in our children who were asphyxiated at birth than in average children tested by Haggerty, Olson, and Wickman.[4]

DISCUSSION

Serious anoxia occurring during pregnancy and labor may be responsible for many stillbirths and neonatal deaths. In addition, a relationship between birth injury and later degenerative lesions in the brain has been reported by many neurologists. Schreiber[11] noted that 70 per cent of a large group of children, having brain defects, were found to have been asphyxiated at birth. Various mechanisms may operate to deprive the fetal brain tissue of oxygen. Barcroft[3] and Peters and Van Slyke[9] have classified anoxia as anoxic, anemic, stagnant, and histotoxic. In anoxic anoxia the arterial blood is insufficiently saturated with oxygen. Anemic anoxia results when the oxygen-carrying power of the blood is decreased. Stagnant anoxia occurs if less than the normal amount of circulating blood is carried to the cells. Histotoxic anoxia will develop even though the oxygen supply is normal if the cells are so altered that they cannot utilize the available oxygen.

During pregnancy one or more of these mechanisms may operate to produce anoxia. Premature separation of the placenta, placental disease, nitrous oxide anesthesia given for minor operations, pneumonia

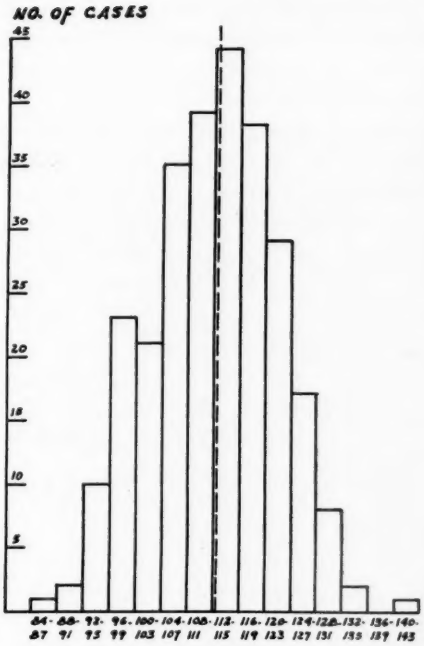

Fig. 1.

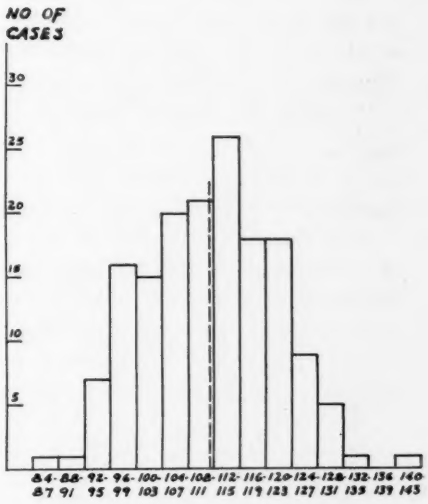

Fig. 2.

Fig. 1.—Histogram showing distribution of I. Q. for entire group tested (270 cases); median 112.4 (dotted line), average 111.4.

Fig. 2.—Histogram showing distribution of I. Q. for "no analgesia group" (159 cases); median 111.7 (dotted line), average 110.8.

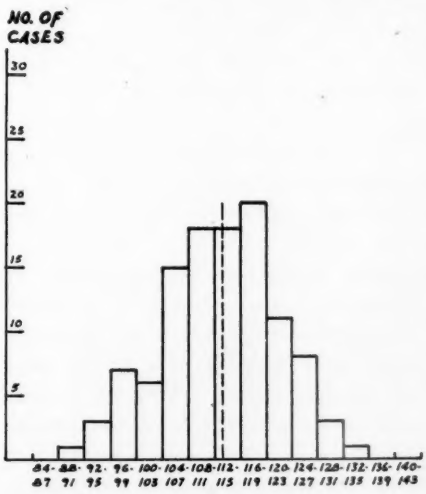

Fig. 3.

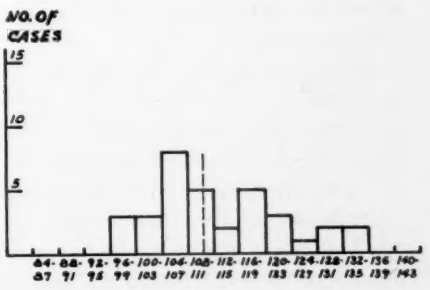

Fig. 4.

Fig. 3.—Histogram showing distribution of I. Q. for "analgesia group" (111 cases); median 113.2 (dotted line), average 112.3.

Fig. 4.—Histogram showing distribution of I. Q. for "asphyxiated group" (34 cases); median 110.4 (dotted line), average 112.1.

with inadequate aeration or the use of sulfanilamide and other drugs which reduce the oxygen carrying power of the blood may contribute to intrauterine anoxia. Eclampsia with its resultant physicochemical alteration of the cell may interfere with cellular oxidation.

Anemia may be an important factor in producing anoxia at any time during pregnancy or labor. An increase in severe apnea is noted when the maternal hemoglobin is below 11.0 Gm. Our study was made at an altitude of approximately 3,300 feet. It is possible that in lower altitudes a lower level of hemoglobin would be necessary to demonstrate such a high incidence of severe apnea. As a physiologic anemia is frequent during pregnancy, and as inadequate diet, poor living conditions, cardiac disease, or acute infections may be superimposed, a severe anemia may develop. In addition, threatened abortion with hemorrhage or hemorrhage from placenta previa or premature separation of the placenta may rapidly produce severe anemia with resultant anemic anoxia. All anemias of pregnancy should be treated and any patient whose hemoglobin is below 11.0 Gm. should be given blood if the response to medication is slow.

During labor if fever is present, the unusual demand for oxygen may limit the supply to the fetus. Pressure on the cord, a knot in the cord, or tight coils about the neck may also serve to prevent an adequate amount of oxygen reaching the fetus. Any trauma or increased pressure on the baby's head prevents free circulation, and as a result the blood carries less oxygen to the brain and may produce stagnant anoxia with resultant degenerative changes in the cerebral cells. This is perhaps the most frequent cause of neonatal anoxia, as in every labor the baby's head is subjected to trauma during both the first and second stages. If unusual trauma is present, and intracranial pressure increases due to cerebral edema or hemorrhage, localized areas may be deprived of oxygen with resultant necrosis. Hartman[5] has shown that trauma without demonstrable fracture, produces cerebral lesions similar to those produced by other anoxic factors. The normal expellant powers of labor produce a mild concussion. If these powers are abnormally great or if disproportion exists, an increase in the incidence of anoxia would be expected.

Histotoxic anoxia may occur during labor or delivery if dehydration is permitted to develop. Dehydration produces a relative concentration of cellular elements, and as a result the cell does not utilize all the available oxygen. During long or complicated labors every precaution must be taken to avoid dehydration, starvation and fatigue. All of the common drugs used to relieve pain during labor have been shown to increase the incidence of neonatal apnea. Cole and associates[1] have shown that even the use of acknowledged pharmacologic doses of scopolamine, morphine, or the common barbiturates greatly increase the degree of neonatal apnea. This dosage is much less than that generally used for full analgesia in obstetrics. The incidence of apnea was increased in our series even though small amounts of pentobarbital sodium and scopolamine were given. A high incidence of severe apnea was noted in the babies born of mothers who became excited. Regardless of cause,

excitement is one of the first signs of cerebral anoxia. A baby born of a mother showing signs of anoxia would be very likely to be apneic at birth. The question of whether to use analgesic drugs and how much should be used, must be weighed carefully against the possible increased incidence of neonatal apnea and possible destructive cerebral anoxia. If the mother is properly prepared, most labors can be conducted with fair pain relief even though small amounts of analgesic drugs are used. In our series 50 per cent of the patients received satisfactory pain relief. If small doses are used, the undesirable effects of histotoxic anoxia can be reduced.

Fig. 5.—The effect of various obstetric factors in the production of neonatal apnea.

During delivery the use of nitrous oxide-oxygen as an anesthetic agent may produce oxygen want. Murphy[8] states that surgical anesthesia, defined as a state of muscular relaxation with adequate oxygen concentration, cannot be produced by nitrous oxide and oxygen. Eastman[2] has shown that nitrous oxide-oxygen anesthesia given for periods of less than five minutes, and in proportions of 85:15 or weaker, does not cause a harmful degree of anoxia. In the cases presented in this study, 50 per cent nitrous oxide and oxygen, supplemented by local anesthesia, was employed. This method permits the use of nitrous oxide as a relatively weak analgesic agent. If the danger of a harmful degree of anoxia is avoided, the objections to the nitrous oxide-oxygen mixture disappear.

After delivery, anoxic anoxia may occur if the air passages are not clear. Prompt removal of mucus in all babies immediately after birth seems to stimulate respiration, as it is rarely necessary to use a tracheal catheter. Neonatal anoxia may not develop for some hours or days after birth. This type may be due to increased intracranial pressure, a result of cerebral edema or hemorrhage.

Fig. 5, a composite of the tabulated data, demonstrates the influence of various factors in the production of neonatal apnea. The white portion of the bar indicates the percentage of babies crying immediately after birth. The most important factor, trauma, may be produced by abnormal delivery, premature rupture of the membranes, outlet forceps, long second stage, or rapid labor. In premature babies, even a normal delivery may be associated with considerable trauma. Some of the factors producing apnea cannot be avoided but cumulative factors in these patients should be prevented. Maternal anemia should be controlled either by the routine use of some iron preparation or by the use of iron if indicated. Analgesia should be avoided if some uncontrollable factor such as anemia or prematurity is present. If analgesic medication is used an elective operative delivery should be postponed until the effect of the drug used is minimal. Eastman[2] and Henderson[6] have emphasized that the brain tissue of an infant is most susceptible to oxygen want. Yant,[13] Schreiber and Gates,[12] Hartman,[5] and others have shown that lesions in the brain are identical in all deaths from anoxia, regardless of cause. Schreiber[11] believes that even though the symptoms of cerebral anoxia may be alarming, complete recovery of function is possible, providing an adequate supply of air or oxygen is available before prolonged deprivation results in irreversible cellular destruction.

Neonatal apnea cannot be prevented entirely. Eastman[2] has said: "We hold to the belief that asphyxia neonatorum, in all of its manifestations, is an example of profound oxygen want. For this reason the one urgent necessity in its treatment is oxygen, and by the same token, the one urgent requirement in its prevention is oxygen." We have attempted to prevent anoxia by giving oxygen freely during the latter part of the second stage of labor. Every mother is given oxygen as long as the cord pulsates, and if the baby is apneic, oxygen or oxygen and CO_2 are supplied by means of gentle artificial respiration when pulsations in the cord cease. In addition, an attempt is made to reduce the incidence of neonatal apnea by the prevention of anemia and dehydration; by restricting operative procedures to absolute indications; by avoiding early rupture of the membranes if possible; by using only small amounts of analgesic drugs; and by supplementing light anesthesia with local anesthesia.

Intelligence and behavior tests were made on 270 school children in order to evaluate this procedure. Adequate birth records were available for all of these children. The number studied is, as yet, too small to be of statistical significance. The median of the entire group is high when compared with tests on general population groups, which may be partially accounted for by the economic group included in the study. Thirty-four, who had been apneic at birth, had a median I. Q. of 110.4 as compared with a median of 100 in general studies. Of the apneic group, only 3 were below 100. The lowest I. Q. was 97. Five of the 34 had an I. Q. above 125. It is said that an I. Q. above 125 indicates superior intelligence. Even though only a small series has been studied,

it would seem safe to say that the figures do not indicate mental retardation in the apneic group. If such a conclusion is permissible, this preliminary study indicates that apnea may be present at birth without severe anoxia and its resultant cerebral damage, providing oxygen is administered during the apneic period.

CONCLUSIONS

1. Abnormal delivery, prematurity, early rupture of the membranes, outlet forceps, maternal anemia, long second stage, rapid labor, and the use of analgesic drugs are important factors in the production of neonatal apnea.

2. The incidence of neonatal apnea may be reduced by the prevention of anemia and dehydration; by restricting operative procedures to absolute indications; by preserving the membranes if possible; by using small amounts of analgesic drugs; by supplementing light anesthesia with local anesthesia; and by the liberal use of oxygen.

3. The importance of recognizing the factors frequently associated with neonatal apnea is stressed so that we may avoid, if possible, superimposing factors which would tend to increase the incidence of serious cerebral anoxia.

4. Two hundred and seventy school children were studied, using standard intelligence and behavior tests. At birth each of these children had received oxygen until respirations were established and until the color remained pink. The data tend to show that the few babies who were apneic at birth, did not show evidence of mental retardation when they reached school age.

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DISCUSSION

DR. OTTO H. SCHWARZ, St. Louis, Mo.—Dr. McPhail shows very conclusively that there is increase in the asphyxia during analgesia. He also states that he does not carry this analgesia out to the extent where amnesia is to be expected, although a certain percentage of his patients have complete amnesia.

In St. Louis for a number of years, we gave analgesia excessively. We started in 1915 and used the original method of Gwathmey and continued using that method until about eight or nine years ago when we substituted barbituric acid by mouth. Recently we have been using seconal, 1½ to 3 gr., with scopolamine. The seconal

allows us to reduce the scopolamine by half and get the same amount of amnesia. Some of the men are still using small doses of morphine, but most of us have eliminated morphine entirely.

It is my experience that the analgesia is not necessarily the cause of the asphyxia. It is more likely to be due to the general anesthetic which is given at the time of delivery. We have used chloroform for a long time, and I believe from the work of Eastman that chloroform has less asphyxiating effect than any other anesthetic. The trick is to give chloroform openly and slowly. With the combination of scopolamine, the barbiturate and this general anesthetic we see very little asphyxia. Nitrous oxide given at the time of delivery has shown a very definite increase in asphyxia.

So far as the question of the intelligence quotient of these children is concerned, I think what Dr. McPhail has brought out is just about what one would expect. When we started using twilight sleep we were criticized because of the aftereffects on the child, but on account of its transitory character, I always felt there would be no permanent effect either on the mother or the child.

DR. GEORGE W. KOSMAK, NEW YORK, N. Y.—In New York we have become interested lately, through a report from the Health Department, in the enormous problem of the crippled child in the educational system. A study was made of these crippled children over a period of three to five years and an attempt was made to develop some knowledge as to the causation of these conditions. The obstetric influence in this investigation was not a very important or definite one, because the entire subject was dismissed with the statement that in one-third of all these cases birth trauma was given as the cause of the crippling.

A few of us rather demurred at that wholesale designation, and we have appointed in the Academy of Medicine a Committee to study this entire subject of congenitally crippled children through the medium of a group that includes the obstetrician, neurologist, pediatrist, and orthopedist. It was found that in this survey about three-tenths of those under investigation had developed cerebral palsy. Now it is easy enough to ascribe the development of cerebral palsy to obstetric injury if the mother is simply asked whether she had a forceps delivery. Of course, nowadays a large proportion of women are delivered by instrumental means, and it is hardly fair to attribute the occurrence of cerebral palsy to the trauma at birth simply by asking that one question.

What Dr. McPhail has said about the aftereffects on the future intellectual life of the child is very important, and I think we must solve the problem of the occurrence of such crippling conditions by a much wider investigation. Several of the men who came into these conferences admitted quite freely, men who had large experience with cerebral palsy, that trauma did not enter into the problem at all.

Unfortunately, these children do not die at an early age, and there is little possibility of getting autopsies, but the men who have observed these children came to the conclusion that in many of the cases we were not dealing with any injuries that could be attributed to the labor but rather with some shortcomings in the development of their nervous systems. So, while Dr. McPhail's observations are of great interest, I do not believe they will help us a great deal in any attempt to find the underlying causes in such unfortunate conditions as cerebral palsy and similar disturbances. However, I think we should be very grateful if a definite study along the lines he has pursued could be more universally developed throughout the country so that we might get some definite knowledge as to the underlying conditions that develop in these children later in life.

DR. WILLIAM E. CALDWELL, NEW YORK, N. Y.—Dr. McPhail has pointed out that a long, slow labor does not necessarily mean an apneic baby. It is the strong spasmodic contractions of the uterus against the resistance of the soft parts or the bony pelvis that gives apneic babies and birth injuries, especially in premature babies.

Asphyxia per se should increase the fetal heart rate. The slowing fetal heart means that there is obstruction to the fetal circulation necessitating the slowing heart to overcome such an obstruction. With the rupture of the membranes and with the descent of the head into the pelvis, the placental site is greatly com-

pressed, especially at the height of a contraction. Again the cord may be compressed between the child and the birth canal. Occasionally a cord is so tightly bound around the neck or the child's body that further descent obstructs the cord circulation. Obviously the treatment is to relax the uterus, to give the woman oxygen, and to displace the presenting part upward until the fetal heart has returned to its normal rate. In cases where the scalp can be seen, increasing cyanosis, especially when accompanied with a slow heart, calls for oxygen to the mother, relaxation of the uterus, and displacement of the presenting part upward.

To relax the uterus, as has been brought out by Eastman and others, there is no drug that works as well as chloroform. To relieve apnea, as Dr. McPhail has pointed out, pure oxygen inhaled by the mother is essential. We should condemn very strongly the attempts to deliver the mother by forceps while the venous system of the child is markedly congested, especially when the cervix or birth canal is not well retracted over the head. There are too many forceps being used for the immediate extraction of the child for fetal distress.

VITAMIN THERAPY IN VULVAR DERMATOSES*

Components of the B Complex

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THE clinical similarity of mycotic vulvitis to chronic atrophic vulvitis was emphasized in 1937, but the underlying cause for the latter condition was not explained. While pursuing this problem, it became necessary to investigate the influence of at least some of the vitamins, especially factors of the B complex. To 15 cases of chronic atrophic dermatitis of the vulva, 5 cases of an undetermined type of vulvitis and 2 cases of unexplained vulvar pruritus are added to make a total of 22 individuals studied with respect to clinical and symptomatic responses to single and combined factors of the vitamin B complex.

Although unexpected improvements occurred in some, others did not yield to the same therapy. By election this evaluation is concerned with the importance of thiamin hydrochloride (B_1), alone or with riboflavin (B_2 formerly G), nicotinic acid or nicotinamide, pyridoxine (B_6), and calcium pantothenate. The procedure followed on the whole the trial and error method, because so far the enormous literature lacks reference to a concrete program for such an investigation. The dosage needs establishment. Considerable ignorance exists regarding the interrelationship not only of these five members of the vitamin B complex but also of the other B factors as well as vitamins A, C, D, E, and K.

As proposed by Adair and Davis, the term chronic atrophic dermatitis of the vulva is employed at the Chicago Lying-in Hospital to designate chronic atrophic vulvitis, leucoplakic vulvitis, kraurosis in the broad sense, and other such synonyms.

LITERATURE

Microscopic examination makes positive the diagnosis, yet the lucid and photographic descriptions by Taussig, Adair and Davis, and Hunt and Bonney and others offer support to the clinical or macroscopic diagnosis of chronic atrophic dermatitis of the vulva. From two to four stages are recognized by most investigators. Adair and Davis and Taussig agree upon three stages. The importance of differential diagnosis stands out when one notes the unanimity of opinion in the literature. Taussig earlier and then Hunt recorded in detail pathologic and symptomatologic aspects of chronic atrophic vulvitis.

Some differences prevail on the therapeutic approach. Montgomery and Counseller recommend nerve resection, a few counter with nerve blocking much after the pattern of Wilson by alcoholic injection. The majority of gynecologists agree with Adair and Davis, Taussig, Kimball,

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and others in their proposal of surgical removal or adequate vulvectomy. Norris and Block stressed by quotation the benefits gained from hormone therapy. On the premise that achlorhydria and deficiency of vitamin A resulted in the vulvar condition, Swift prescribes dilute hydrochloric acid and vitamin A. Recently Hunt describes secondary pellagrous manifestations closely resembling chronic atrophic vulvitis.

Certain reports indicate that vitamins A and D are related to infections and to leucoplakic change while vitamin C may be correlated with infections alone yet all in all these points remain unsolved. Thus, the magnitude of the field for study becomes apparent.

Special focus upon deficiencies in the components of the B complex as possible etiologic agents for certain conditions of the skin and lesions of the mucous membrane of the mouth came through the observations of Spies, Cooper, and Blankenhorn; Dabney; Landor; and Sydenstricker, Geeslin, Templeton, and Weaver. Lesions not unlike those of the lips and oral cavities were found upon the vulva, vagina, perineum, and also scrotal areas. Dabney relieved idiopathic pruritus vulvae in 4 of 8 patients with nicotinic acid. Landor relied upon riboflavin for therapeutic advantage. Elvehjem challenged with the unmodified statement that each vitamin has a very limited effect on the animal body and can be used with success only when it is lacking. Hastings, Muus, and Bessey agreed with others that the B complex is concerned with oxidation. Thiamin hydrochloride serves as a catalyst of decarboxylation, of oxidation, and of dismutation of pyruvic acid, so avers Gruzman-Barron. These and other references demonstrate that in thiamin hydrochloride deficiency, pyruvic acid content of the blood and urine increases. Pyruvic acid is also one of the by-products of certain yeast-like organisms. Such intermediary products of metabolism, as pyruvic acid, whether excreted in the urine or produced in the genital tract by the medical monilia, might create an opportunity for vulvar irritation. Such a modus operandi might explain certain similarities of mycotic vulvitis and chronic atrophic vulvitis.

The administration of riboflavin alone and with other factors of the same complex causes cheilosis, stomatitis, and glossitis to vanish. Sydenstricker, Kelly, and Weaver warn that under experimental conditions large amounts of nicotinic acid in the presence of deficient diets seem to increase the requirement for riboflavin and to precipitate signs of ariboflavinosis. This indicates the existence of a relationship or balance between these two components. The investigations of Spies, Bean, and Ashe; Spies, Ladish, and Bean; and Spies, Stanbery, Williams, Jukes, and Babcock leave little doubt that pyridoxine (B_6) and pantothenatic acid are essential to human nutrition. It is yet to be established whether a characteristic type of vaginitis or vulvitis may be found in patients with vitamin deficiency diseases. Moreover, the descriptions of perineal and other genital lesions are insufficiently definite to justify critical comparison with the undetermined type of vulvitis and chronic atrophic vulvitis of this series.

Rhoads brought about the disappearance of pathologic and physiologic alterations (leucoplakia) of the oral mucosa with the ingestion of large amounts of yeast. B complex deficiencies produced experimentally by Elson, Lewy, and Heublein improved only partially on thiamin hydrochloride addition, but very little with riboflavin replacement, yet

brewer's yeast relieved the condition completely. However, yeast preparations contain not only factors of the B complex and other vitamins but amino acids. How these amino acids individually or collectively would affect these conditions remains unknown.

Fig. 1.—Patient 20, aged 85. Hyperemia, edema, and altered tissues extend laterally beyond the vulva. Pruritus present for four years. (Reproduced from 35 mm. Kodachrome picture.)

Fig. 2.—After thirty-five days of treatment on average daily intake of 25 mg. of B_1 and 10 mg. of B_2. Slight recurrence on one occasion within past four months but completely relieved by administration of B_1 and B_2. (Reproduced from 35 mm. Kodachrome picture.)

The already heavily burdened pituitary gland received an assignment from Sutton and Ashworth to the effect that an extract of the anterior lobe of the pituitary gland caused recovery of pellagrous lesions when nicotinic acid, riboflavin, parenteral liver, and adequate diet had failed.

Morgan found that when multiple deficiencies exist unfavorable results may follow the administration of a single lacking element.

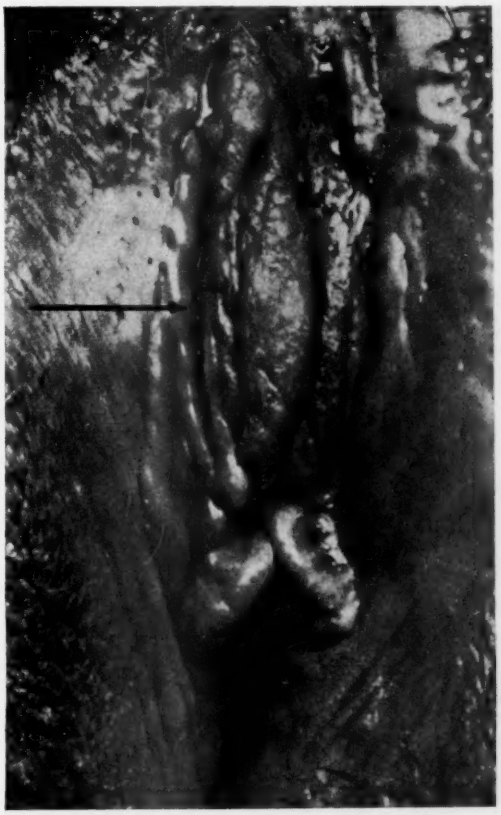

Fig. 3.—Patient 9. Edema, hyperemia, and long interlabial fissures with pruritus as principal symptom. (Reproduced from 35 mm. Kodachrome picture.)

PROCEDURE AND RESULTS

Obviously, the infrequency of undetermined type of vulvitis, pruritus and chronic atrophic vulvitis makes it difficult to accumulate a large number of patients for study. Through the cooperation of the entire staff it was possible to amass 22 cases in a period of approximately three years. The diagnosis was made or confirmed by other members of the staff. As a rule, the diagnosis resulted from inspection and palpation, yet in a few instances biopsies confirmed the clinical impressions. Photographic records on 35 mm. kodachrome film eliminate some error, perhaps, in respect to macroscopic superficial tissue changes subsequent to the administration of the various preparations. Reproductions in color or black and white prints from the original colored photographs have been unsatisfactory generally because of some technical

difficulties in photography. The treatment consisted solely of the administration of vitamins. Other general and all local therapy were excluded and even the diet and habits in general were unaltered intentionally.

In undertaking a study of the B complex one is faced immediately with at least 5 chemically pure substances. The order, the dosage, the route of administration, and the relationship to other components of

Fig. 4.—After forty-two days of treatment, fissures closed, hyperemia and pruritus absent. Averaged daily 50 mg. B_1 and 14 mg. B_2. (Reproduced from 35 mm. Kodachrome picture.)

the group made for complexity of the study. Moreover, remissions or variations of chronic atrophic vulvar dermatitis and of undetermined vulvitis would nullify minor or temporary changes, presumably resulting from any therapy.

The oral route of administration was used almost exclusively for this series. Parenteral administrations might well be investigated subsequently. As has been pointed out, deficiency of thiamin hydrochloride may result from (a) inadequate diet, (b) inadequate absorption, (c) improper utilization, (d) faulty liver function, (e) vascular disease, and (f) prolonged infections.

The general plan called for the use of thiamin hydrochloride (B_1) orally in dosage varying from 5 to 80 mg. daily, but tending toward larger amounts. The first few patients received, often, proportionately smaller amounts, but as clinical and symptomatic reaction seemed, at times, to be related to larger amounts, more was given. Lacking clinically usable tests, guidance came from clinical and symptomatic response.

According to the usual standards, 19 of the 22 patients were free apparently of vitamin deficiency; of the remaining 3, one existed on an inadequate diet, one most likely had a faulty or inadequate absorption, and the third one suffered from a protracted and unusual infection with

Fig. 5.—Patient 15. Leucoplakic-like lesion between clitoris and urethra. (Reproduced from 35 mm. Kodachrome picture.)

multiple draining areas. Table I lists those receiving thiamin hydrochloride alone in relation to dosage, age, stage and type of lesions, length of therapy, and results. Of the 11 cases of leucoplakic vulvitis, 4 were alleviated; 1 remained unchanged; the leucoplakic area and symptoms disappeared in 1 case but the vitiligo persisted. The remaining 5 were improved from a moderate to a considerable degree. The unalleviated patients are still under observation. The word "alleviated" expresses the idea of apparent cure, but sufficient time has not elapsed to establish this point.

If the lesions were manifestations of pellagra then nicotinic acid or nicotinamide should bring about improvement if not a cure. At least

TABLE I. THIAMIN CHLORIDE (B_1) ONLY IN VULVAR DERMATOSES

PATIENT	AGE	VULVAR DIAGNOSIS	STAGE	DAILY DOSAGE MG.	DAYS TREATED	CLINICAL AND SYMPTOMATIC RESULTS
3	47	Vulvectomy 1 yr. prior; chr. atrop. derm.	3	20	42	No change†
4	39	Chr. atrop. derm.	3	80	21	Improved symptoms only
5	49	Chr. atrop. derm.	1	10-30	42	Mod. improvement; poor co-operation
6	58	Chr. atrop. derm.	3	20-60	56	Lost leucoplakia and sympt.; vitiligo unchanged
7	57	Chr. atrop. derm.	2	20	14	Mod. improvement†
10	63	Chr. atrop. derm.	1-2	60-80	35	Improved markedly
11	47	Chr. atrop. derm.	1	20-30	56	Alleviated
12	43	Chr. atrop. derm.	1	20-40	42	Alleviated
13	42	Chr. atrop. derm.	1	20	28	Alleviated
14	43	Chr. atrop. derm.	1	10	21	Alleviated
15	47	Chr. atrop. derm.	1-2	40-80	14	Alleviated
19	64	Vulvitis (undet.)		20-80	14	Improved*
21	43	Vulvar pruritus (undet.)		5-15	56	Alleviated
22	43	Vulvar pruritus (undet.)		40	7	Improved

*Followed with $B_1 + B_2$.

†Followed with TRN6P (thiamin, riboflavin, nicotinamide, pyridoxine and pantothenate combined in tablet).

TABLE II. NICOTINIC ACID OR NICOTINAMIDE ONLY IN VULVAR DERMATOSES

PATIENT	AGE	VULVAR DIAGNOSIS	STAGE	DAILY DOSAGE	DAYS TREATED	CLINICAL AND SYMPTOMATIC RESULTS
2	42	Chr. atrop. derm.	2	200 mg.	21	Relapsed under treatment
4	39	Chr. atrop. derm. with vitiligo	3	200 mg.	28	Relapsed under treatment
5	49	Chr. atrop. derm.	1	225 mg.	21	Relapsed under treatment
16	46	Vulvitis (undet.)		200-300 mg.	21	Unchanged
19	64	Vulvitis (undet.)		200 mg.	14	Unchanged

Thiamin Hydrochloride (B_1) and Riboflavin (B_2) in Vulvar Dermatoses

				B_1	B_2		
2	42	Chr. atrop. derm.	2	20-30	2-5	14	Unchanged*
8	52	Chr. atrop. derm.	2	80	10	21	Marked improvement
9	58	Chr. atrop. derm.	1-2	40-60	8-20	42	Marked improvement
16	46	Vulvitis (undet.)		80-60	20-10	21	Unchanged
19	64	Vulvitis (undet.)		80-40	20-10	21	Marked improvement
20	85	Vulvitis (undet.)		30-20	10	35	Alleviated

*Followed by TRN6P (thiamin, riboflavin, nicotinamide, pyridoxine, and pantothenate).

in the 5 (Table II) subjected to such treatment there was hardly a suggestion that these patients were pellagrins, for the 2 with vulvitis were unaffected and the 3 with chronic atrophic vulvitis had only slight symptomatic improvement which shortly reverted to the original state.

As had been the plan, other components of the B complex were added when improvement failed or did not progress satisfactorily. Thus, riboflavin (B_2) next came to trial in combination with thiamin hydrochloride (Table II continued). The fact that stomatitis, glossitis, and cheilosis vanish with adequate amounts of riboflavin might suggest

that this factor should be tried individually; and later a trial will be given to it alone. From these 6 cases, 2 were refractory to this management; 1 with a chronic atrophic vulvitis and 1 with undetermined vulvitis. One undetermined vulvitis was alleviated while 1 improved. Two cases of chronic atrophic vulvitis showed improvement. These 3 improved cases now appear to be well on the way to an apparent cure. One patient, aged 85 years, had a niece 64 years of age and both had an unexplained vulvitis, which was rather similar, yet they had apparently adequate diets and lived in different communities.

Fig. 6.—Condition and symptoms alleviated in fourteen days. Average daily intake of B_1 60 mg. (Reproduced from 35 mm. Kodachrome picture.)

To combine the other three factors with B_1 and B_2 might shorten the study. A tablet with five factors was available. It contained 5 mg. of thiamin hydrochloride, 5 mg. of riboflavin, 25 mg. of nicotinamide, 5 mg. of pyridoxine (B_6), and 25 mg. of calcium pentothenate.* The daily dosage varied from 3 to 6 tablets but was usually 4. Most of the patients were given additional B_1 to make a daily total of B_1 from 60 to 100 mg. Seven patients on this combination gave varied and unexplained responses (Table III). Both patients who had had recurrence after vulvectomy, improved symptomatically, while the tissue changed only by regression of hyperemia and healing of fissures, but the atrophic state and vitiligo persisted. One patient has been a frank failure so far.

*This and the other vitamin preparations were supplied by Merck & Company.

Three had definite improvement and 1 was alleviated. This special tablet is not commercially available, but its equivalent can be obtained by the administration of sufficient amounts of each of these substances.

Perhaps a better picture may be had through a composite table (Table IV) which indicates the order and type of combinations given to each patient. As one might expect the Stage I chronic atrophic dermatitis of the vulva improved more dependably than the more severe and also the more chronic ones in which considerable alteration of tissue had taken place. One of the undetermined type of vulvitis group was alleviated, 3 improved, and 1 unchanged. According to the present observations Patient 19 might attain alleviation. Possibly 2 might

Fig. 7.

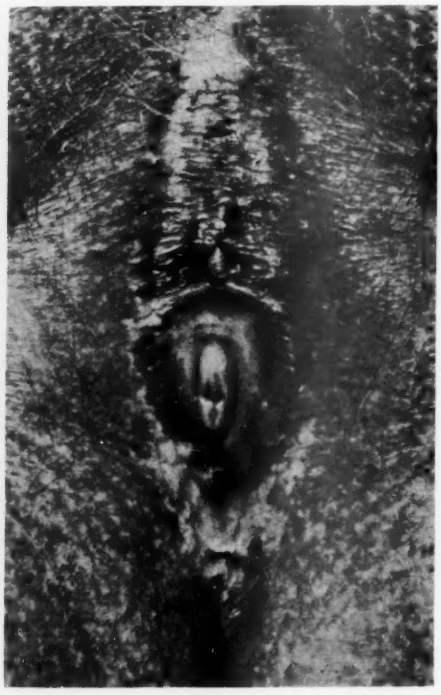

Fig. 8.

Fig. 7.—Patient 6. Biopsy of edge of perineal lesion confirmed diagnosis of leucoplakic lesion in chronic atrophic vulvitis. Note vitiligo above clitoris and on labia majora and perineum. (Reproduced from 35 mm. Kodachrome picture.)

Fig. 8.—Leucoplakic lesion and pruritus absent but vitiligo and atrophic change unaltered. Treated fifty-six days, average daily intake 40 mg. of B_1. (Reproduced from 35 mm. Kodachrome picture.)

be classed as chronic atrophic dermatitis, but infections resulting probably from the trauma of scratching made it obligatory to place them in the class of undetermined. Pruritus is entirely subjective and hence not reliably evaluated by observations. Such symptoms lend their course to many influences.

Some patients have been maintained on one or another of the vitamin B complex for considerable periods without evidence of intoxication, but further observations are imperative to verify the safety of this practice. If such large amounts are actually necessary, perhaps the

TABLE III. COMBINATION OF CERTAIN B COMPLEX FACTORS ONLY IN VULVAR DERMATOSES

TRN6P (Each tablet contains thiamin 5 mg., riboflavin 5 mg., nicotinamide 25 mg., pyridoxine 5 mg., Ca. pantothenate 25 mg.) – X

PATIENT	AGE	VULVAR DIAGNOSIS	STAGE	DAYS TREATED	CLINICAL AND SYMPTOMATIC RESULTS
1	68	Chr. atrop. derm.; vulvectomy 2 yr. prior	3	91	Symptoms improved; tissue unchanged
2	42	Chr. atrop. derm.	2	35	Unchanged
3	47	Chr. atrop. derm.—Perin.; vulvectomy 1 yr. prior	3	84	Symptoms improved; tissue unchanged
7	57	Chr. atrop. derm.	2	98	Improved
14	43	Chr. atrop. derm.	1	42	Alleviated
17	39	Vulvitis (undet.)		42	Improved; poor cooperation
18	31	Vulvitis (undet.)		28	Improved; poor cooperation

X = 3 to 6 tablets daily and usually enough more thiamin added to give total of 60 to 100 mg. daily.

TABLE IV. TREATMENT BY VARIOUS FACTORS OF THE B COMPLEX

PATIENT	AGE	STAGE	N***	B_1†	B_1 & B_2‡	TRN6P§	DAYS TREATED	CLINICAL AND SYMPTOMATIC RESULTS
Chronic Atrophic Vulvar Dermatitis								
1	68	3**	*			1	98	Sympt. slightly impr.; tissue unch.
2	42	2	1		2	3	70	Unchanged
3	47	3**		1		2	126	Symptoms impr.; tissue unch.
4	39	3	1	2			49	Impr. symptomatically only
5	49	1	2	1-3			63	Improved
6	58	3		1			56	Lost leucoplakia and sympt.; vitiligo unchanged
7	57	2		1		2	112	Improved
8	52	2			1		21	Improved markedly
9	58	1-2			1		42	Improved markedly
10	63	1-2		1			35	Improved markedly
11	47	1		1			56	Alleviated
12	43	1		1			28	Alleviated
13	42	1		1			28	Alleviated
14	43	1		1		2	63	Alleviated
15	47	2		1			14	Alleviated
Vulvitis (Undetermined Type)								
16	46		1		2		42	Unchanged
17	39					1	42	Improved; poor cooperation
18	31					1	14	Improved; poor cooperation
19	64		2	1	3		49	Improved markedly
20	85				1		35	Alleviated
Pruritus								
21	43			1			56	Alleviated
22	43			1			7	Improved; poor cooperation

*1, 2, 3, etc., order in which used. **Vulvectomy previously for chronic atrophic vulvar dermatitis. ***N, Nicotinic acid or nicotinamide.

†B_1 Thiamin Hydrochloride.

‡B_2 Riboflavin.

§TRN6P (Each tablet contains thiamin 5 mg.; riboflavin 5 mg.; nicotinamide 25 mg.; pyridoxine [B_6] 5 mg.; and Ca. pantothenate 25 mg.) usual extra B_1 given.

action is pharmacologic rather than strictly a vitamin response. If large doses are required the mixed proprietary products on the market would appear impotent or of very limited value because of their minute amounts, but proof is not yet forthcoming.

SUMMARY

These observations are presented for their scientific value alone. The data show that management as outlined above did not eradicate vitiligo or correct advanced (Stage 3) chronic atrophic dermatitis of the vulva although symptoms may be partially or completely relieved and fissures and leucoplakic areas may disappear. On the other hand the first stage of chronic atrophic vulvitis and certain other types of undetermined vulvitis may vanish with the administration of thiamin hydrochloride, thiamin hydrochloride and riboflavin, or multiple factors of the B complex. This difference may be anticipated because response should be more likely before extreme tissue damage has occurred. When prescribing factors of the B complex, sufficient amounts are indicated and a balance or relation of the factors may be necessary.

A tendency existed for recurrences in a few of the alleviated patients, possibly because of premature withdrawal of the vitamins, possibly because of some imbalance in the metabolism other than a deficiency disease process, or possibly because of some other state. Small doses may be needed for an indefinite period for some who responded to this management, but as yet a conclusion cannot be made.

Although alleviations (presumable cures) transpired under the administration of factors of the B complex, these conditions have not been classed as manifestations of deficiency diseases.

Moreover, one should not attempt such therapy for chronic atrophic dermatitis of the vulva unless one is prepared to observe and follow the case for a sufficient length of time in order to establish satisfactory benefit to the patient or institute appropriate therapy such as vulvectomy, lest a malignancy develop. Such management is not yet endorsed except for individuals in such poor health that surgery would not or should not be done and for those cases of vulvitis for which an established therapy is wanting. If the distress of chronic irritation can be relieved perhaps the incidence of malignancy might be reduced.

The need for more and properly controlled studies for evaluation of these vitamins becomes evident especially to guard against their misuse and abuse as well as to render better care for patients. Caution is stressed in the use of the vitamins.

Appreciation is expressed for the thoughtful cooperation of the members of the department in this investigation and also for the valuable aid of Merck & Company in supplying the vitamin preparations.

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DISCUSSION

DR. FRED J. TAUSSIG, ST. LOUIS, MO.—I have for many years sought to relieve cases of leucoplakic vulvitis and pruritus of the vulva by various nonsurgical procedures. Ointments were found to be of little, even palliative, benefit. Ovarian therapy, on the other hand, particularly since we have obtained more powerful products, such as stilbestrol, seems in a limited group of cases to have not only caused relief of symptoms but also to produce temporarily marked improvement in the vulvar skin. Those with less advanced lesions, in the so-called hypertrophic stage of leucoplakic vulvitis, show a higher percentage of relief.

Many years ago I had a patient with well-developed kraurosis, who refused operation and later went to a general practitioner who put her on a low-protein, high carbohydrate diet with complete relief of symptoms and marked local benefit. Through other members of the family I learned that she remained well for three years, when she died suddenly of apoplexy. Many of these women are advanced in years and not good operative risks, so that a nonsurgical treatment is worth consideration.

I have tried Swift's method of giving dilute hydrochloric acid with vitamin A in four or five cases but without any success. Thus far my experience with vitamin B complex is too recent to justify any opinion as to its efficacy.

A definite leucokraurosis is so frequently the forerunner of cancer, that surgical ablation of the vulva and, if necessary, of the perianal skin, should in my opinion alone be considered. In my recent report on cancer of the vulva, I discussed several cases of leucoplakic vulvitis, that were not kept under close observation and later returned with a well-developed cancer. Any nonsurgical procedures therefore that give temporary relief may lull the patient into a state of false security. Such individuals must be told to report for re-examination every four to six months for the rest of their lives, since the atrophic brittle skin is constantly subject to minute abrasions and cracks, from which a malignancy may develop.

Of course we know little or nothing about the whys and wherefores of vitamin therapy and all apparent results must be analyzed with the greatest skepticism, but the history of medicine is full of examples of a proved therapeutic agent found long before the manner of its action has been discovered. In view of the relative infrequency of these chronic atrophic lesions of the vulva, I would suggest that in the earlier cases a more extensive trial be given of this method of treatment with vitamin B complex in the dosage recommended by Dr. Hesseltine, so that we can arrive at some opinion of its value in the course of the next five years.

(The remaining papers presented at the Sixty-Sixth Annual Meeting of the American Gynecological Society will be published in the November issue.)

Special Article

DEVELOPMENTS AND TRENDS IN GYNECOLOGY*

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I SHALL not attempt in a short address to cover the history of gynecology. It would be a futile endeavor, and besides I am sure that you are all familiar with the high lights of the history of your science and art. My task will be different. Taking gynecology as my subject, I would like to make a few general historical remarks and would like to show you that there are two aspects of the history of medicine. Unless we consider them both, we shall never attain to a comprehensive picture of developments. There are actually two histories of medicine. One is the history of medical science. It teaches how man gradually discovered the structure of the human body, the function of its organs, disease mechanisms, methods to diagnose disease conditions, to evaluate them in making a prognosis, and finally methods of treatment. The more knowledge man had, the more effective his weapons became in the prevention and cure of illness. This, however, is only one side of the picture, and there is another aspect to it, the social and cultural history of medicine. Knowledge alone is not enough. It does not become effective unless we are able to apply it. Society must be ready to accept the physician's advice, and here we find that religious and philosophic views, social and economic conditions had a tremendous influence and largely determined success or failure of medicine.

There is another point that must be taken into consideration. Scientific research was applied to subjects that seemed important at the time. Valuations changed a great deal and were also determined by nonmedical factors. Modern pediatrics could not develop before chemistry had reached a certain level, but it could not develop either before it had been recognized that the child is more than a small-sized adult, and before the position of the child in society had changed. This likewise was the case with gynecology. The attitude of society toward woman and her position in the social structure were just as important factors in the history of gynecology as medical science. I would like to illustrate this by going with you rapidly through the various periods of history.

A determining point in the history of gynecology is to be found in the fact that sex plays a more important part in the life of woman than in that of man, and that she is more burdened by her sex. Nature has imposed menstruation upon her, the long period of pregnancy, the pains of childbirth, and the period of nursing. This explains two basic attitudes. Woman is periodically weakened by her sex life and in need of protection. She becomes dependent on somebody else, and this opens the door to exploitation. The history of exploitation of woman by man is endless. Whoever has traveled in the eastern Mediterranean countries

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remembers the familiar sight of a woman marching with heavy loads on her head and arms, followed by her husband and lord riding comfortably on a donkey and smoking a cigarette. Even in our own society we discriminate constantly against women, paying them lower wages than men for equal work. We discriminate against married teachers and against women students and physicians even in our own medical schools and hospitals.

On the other hand, woman by giving birth to life became an object of worship. She is fertile like the soil. It was known that seed was needed for the plant to grow, but wherever the soil was fertile vegetation was found. The mystery of creation takes place in woman as it does in nature. Nature was worshiped, and so was woman. The Great Mother was a deity found in the earliest civilizations. Neolithic statuettes have been excavated representing a woman that consists of nothing but sex, and there can be hardly any doubt that they represent a deity. In some tribes the dead were buried, their heads covered with cowry shells. The shells were the symbol of the female genital organs, of the door to life. The shell caps were meant to help the dead in coming back to life again. This function of woman as the creator of life gave her prestige, and power at times, which explains why matriarchy was the social organization of many early tribes.

The fertility of man was rarely questioned, and even today when a family has no children the wife is suspected first, and it is difficult to convince a husband that he may be responsible for the condition.

The fact that the mystery of creation takes place in woman led to the view that the womb must be an organ of a special kind. The uterus was frequently viewed as a living organism of its own, endowed with independent motions, with desires and whims. One of our oldest medical documents, the gynecologic papyrus of Kahun written in the third millennium B.C. describes the uterus as being irritated or sluggish or wandering to places where it does not belong. All these conditions were considered to be causes of disease. The word hysteria that we still use means nothing else but the disease of the hystera, which is the Greek word for uterus. In a medieval incantation that I found in a tenth-century manuscript the exorcising priest addresses himself to the uterus, conjuring it to remain in the place destined for it by God and not to wander through the human body causing disease. In votive offerings the womb was frequently represented as an animal, chiefly as a toad. Even in rational therapy certain procedures such as fumigations with odoriferous drugs were meant to "please" the organ.

Because sex played such an important part in woman's life, and because new life came from her, more taboos were imposed upon her than upon man. In all ancient cults woman was considered unclean during her periods, during childbirth and in childbed. As long as she was unclean, she was not permitted to enter the temple, and her condition was considered contagious until she had undergone purification. This gave her an isolated position in society. The concept of cleanliness was purely spiritual, but it had hygienic consequences in that it protected woman against sexual intercourse during menstruation and during the period of involution. These old views, familiar to us from Leviticus, are still alive, not only among Jews but in the whole Mohammedan world. I heard in Bosnia that women there are not allowed to give birth to children in the house, since this would make it impure. They go to the stables where the child is born between a cow and a goat, and infections result quite frequently.

Childbirth was considered a physiologic process and was therefore not an object of medicine. In primitive society a woman, when her hour had come, went into the bushes or to the river, and came back after a while with the newborn infant. If help was needed, it was given by a fellow woman who had gone through this experience herself and therefore knew about it. This still happens today all over the world. And when women began to give this aid professionally, they became midwives. The institution of midwifery has played an extraordinarily important part in the history of medicine. Until a few centuries ago, the midwife was the gynecologist and obstetrician of society. She had empirically acquired knowledge and skills, and in addition was the confidante of women. She, and not the physician, was consulted by women in all matters of sex.

Having been trained in Europe where the institution of midwifery is still firmly established, I have a high respect for the work of these women. I have seen them in action in mountain villages of the Caucasus and among African tribes. As long as society cannot provide a trained obstetrician for every woman, the midwife still has an important part to play, and there are conditions where she can achieve more than the physician. She has more time to spend with the woman in labor, and is frequently closer to the people, one of them, speaking their own language and familiar with their customs.

We do not know when gynecology became a part of medicine. No date can be set for it. As soon as man began to observe symptoms of disease and to reason about them, he saw that women were suffering from pains peculiar to them, from fluxes, discharges, and swellings, that their periods were irregular and that childbirth was not always a physiologic process. Egyptian papyri and Babylonian cuneiform tablets all mention gynecologic symptoms and treatments. Magic took a relatively important part in this field of medicine. Amulets were worn. No Egyptian woman would enter labor without having a statuette of the hippopotamus-shaped goddess Thoeris near by. Amulets are still worn by women in childbirth today. The old idea that in such moments people are the easy target of evil spirits still persists. From Herodotus we know that Egyptian medicine at his time was highly specialized, that there were specialists for every organ and every disease. We do not hear of specialists for the female organs, for the good reason that these organs and the diseases of women were the midwife's domain. She was the specialist.

In ancient Greece the social position of woman varied a great deal according to tribes. Among the Dorians of Sparta girls took an active part in the physical exercises of boys. They were trained to be mothers of soldiers. Conditions were different among the Ionians where the girl grew up in the house, was veiled in the streets and was married by her parents. She attended to the household duties, and the midwife was her gynecologist.

In the fifth and fourth centuries B.C., there was a movement toward emancipation. Plato postulated equal rights and equal duties for men and women including the duty to go to war. Aristotle considered woman an inferior being, an incomplete man, but he too wanted to see her social position improved. Increased attention was paid to women and their ailments, and the Hippocratic writings reflect this trend. Physicians as a rule did not treat gynecologic diseases, but they studied and discussed them. More and more frequently midwives consulted with physicians in difficult cases. From Hippocrates to Alexandria to Rome

and Soranus women's diseases appear in the medical literature, and there is no doubt that the Greek and Roman physicians had considerable knowledge in the field. Many symptoms have been described correctly, and diseases were treated with diets and drugs. Operations were performed, such as embryotomy and the podalic version.

One point must be discussed particularly, because it presents some problems, namely, the ancient attitude toward abortion. The Hippocratic Oath forbids the physician to practice abortion. This is a rather startling prohibition because we know that abortion was practiced very frequently throughout antiquity and that it was recommended by philosophers as a method of regulating the population. Weaklings and crippled infants were destroyed without hesitation, and it is difficult to understand why there should have been any inhibition in the case of abortion. I know only two possible explanations. The Oath seems to be a very old document reflecting conditions when medicine was a secret family lore. The Oath may have been close to certain religious movements, such as Orphism, which forbade the destruction of life in any form. Another possibility is that the physician was forbidden abortion because he should leave it to the people whose business it was, namely, the midwives, just as the Oath forbade the physician the practice of surgery.

The situation changed completely with the advent of Christianity. Christianity came into the world as a religion that promised healing and redemption, both spiritually and physically. It addressed itself to the weak and sick, to the cripple and sinner, and it gave the sick man a preferential position in society. It was declared the duty of society to attend the sick, and nursing developed as never before. The attitude toward pagan medicine was by no means friendly in the beginning. As a religion, Christianity was primarily interested in the health of the soul, and a great deal of interpretation was required to justify care of the body, and to reconcile the new creed with ancient science.

The attitude toward woman was by no means favorable for the development of gynecology. Man and woman were declared equals before God, spiritually, in the hereafter, but otherwise woman was considered an inferior being. Man was made from earth, but woman from man's rib. Sin had come into the world through Eve. Her sin was responsible for the pains of love and for the pains of childbirth. A church father called woman *janua diaboli*, the door to hell.

These views also influenced the attitude toward sex. The Greeks had taken sexual intercourse for granted and had looked at it as a physiologic process that was recommended sometimes for reasons of hygiene. Christianity considered sexual intercourse sinful unless it was performed by married persons with the definite purpose of procreating children. Origenes went so far as to postulate that it should be performed dispassionately, and that even then it should not take place in a room where people pray. The soul counted and salvation was the purpose of life. Abortion was considered murder of a particularly vicious kind, because it prevented a human being from being baptized. Faced with the alternative of saving mother or child, the physician was to sacrifice the mother without hesitation since the mother was already baptized and prepared for the hereafter, while the unbaptized child would be relegated to limbo. Contraception was even worse because it prevented the creation of a human being. Christianity set rigid taboos on sexual matters, under which the Western World had to suffer for a long time.

There was woman-worship in the Middle Ages too. There was a cult of Mary, but Mary was a virgin who had conceived without sin. There was a cult of woman in chivalry, but it was short-lived, had pagan elements, and was limited to a small group. Throughout the Middle Ages woman was relegated to the home and kept subservient to man.

Such conditions were not favorable for the development of gynecology, and hardly any progress was achieved during the period. Practices followed traditional lines and consisted of ancient reminiscences. Gynecology and obstetrics were in the hands of midwives. The *Mulieres Salernitanae* were midwives, specialists in the treatment of women's ailments. Literature consisted mostly of catechisms, from that of Mustio in the sixth century A.D. to the Rosengarten of Rösslin in 1513.

A revolution was created in the Renaissance in this, as in other cultural fields. A new world developed in Western Europe which was very different from the static world of the Middle Ages with its rigid regulations. The new world appealed to the individual in man and called for free competition and free initiative. The attitude toward woman changed, and voices were heard calling for her liberation. The great humanist Erasmus of Rotterdam in one of his Colloquies has a woman say: "Men are tyrants . . . They use us as toys . . . They make us their laundresses and cooks and take great care to exclude us from all other functions. Let them keep for themselves the tasks of government and war, but the mother should at least have a vote when it comes to establishing her children." Another humanist, Cornelius Agrippa, in a Latin *Disquisition on the Nobility and Preexcellence of the Female Sex,* published in Antwerp in 1529, went even further when he said: "Acting against all divine law, violating with impunity natural justice, the tyranny of man has deprived woman of the liberty with which she was endowed at birth. . . . As a child she is kept idle in the home. As if she were unable to attend to any higher function she is not permitted to touch anything but needle and thread." Yet she has a claim to rights. Her part in the bearing of children is much more important than that of man. She nourishes those fragile little creatures and attends to their development. And is she not just as intelligent as the other sex? She has even more insight and acuteness of spirit. Guided by an instinct which is a privilege of her nature, she often sees things more correctly than philosophers and scholars.

With this scientific and social background gynecology could not but progress. In the sixteenth century the foundation of a new descriptive, systematic human anatomy was laid. All the anatomists of the time studied the female organs. Leonardo's drawings of the child in utero were the first to break a long tradition of diagrammatic pictures that illustrated catechisms from Mustio on. Vesalius observed that the pelvic bones do not separate in childbirth. Falloppio described the tubes; Aranzio observed deformities of the pelvis.

On the basis of this new anatomy a new surgery was born, and this immediately benefited obstetrics and gynecology. In France, Ambroise Paré became not only the "Father of Surgery" but was also greatly interested in obstetrics and called himself not only a surgeon but also an *accoucheur.* He and his disciple Guillemeau practiced podalic versions, induced premature labor in cases of hemorrhage, and sutured the perineum. Cesarean section had been practiced on the dead for centuries, ever since an old Roman law had prescribed that no pregnant woman might be buried without having the child removed. But now the operation was practiced on the living woman, not by sow gelders as the

legend had it, but by the ablest surgeons. Guillemeau describes five cases of cesarean section, two of which he performed himself in the presence of Paré, while three were performed by others. They were all fatal. The time was not yet ripe for major abdominal surgery.

Midwives were still the chief practitioners of obstetrics and gynecology, but they were pledged frequently to call the surgeon in difficult cases. Many were in the service of the cities and their profession was regulated strictly. They were examined and had to follow fee schedules. In the sixteenth century the city of Ratisbon established old age and disability pensions for midwives.

The seventeenth century was a period of great tensions and contrasts. While Descartes inaugurated a period of rationalism, the Counter-Reformation was launched, religious intolerance flourished, Campanella was tortured, and Giordano Bruno burned at the stake. At the same time, when absolutistic government prevailed in France, Spain and a number of other countries, democracy developed in England and Holland. In France women became more and more articulate, claiming access to higher education. It was the time when Molière wrote his *Femmes Savantes* and his *Précieuses Ridicules.* The Salon flourished in France where scientists were invited to present their discoveries before an audience of men and women. It was a mechanical age. Mathematics were highly cultivated, and the names of Descartes, Pascal, Leibnitz, and Newton remind us of the great progress achieved in this field. In physics, dynamics and particularly hydrodynamics were in the foreground. Practical necessities forced scientists to take up these studies. Waterways were the chief highways of traffic. The journey from Constantinople to Venice was three times longer by land than by sea, and while the two-wheeled oxcart could not carry more than 2 tons of goods, the average-sized ship transported more than 600 tons. All these trends reflected themselves in medicine, and in gynecology also.

In the seventeenth century, anatomy became *anatomia animata,* dynamic anatomy. William Harvey founded a new physiology, but he was an embryologist also. Embryology is another form of dynamic anatomy. Embryologic studies greatly benefited gynecology. Van Horne declared that the female testicles contain ova. Steno gave the ovaries their name, and de Graaf wrote a classical monograph on the female genital organs, in 1672. In 1677 the spermatozoa were seen.

France had its great century, the Siècle de Louis XIV, and the leading gynecologist was Mauriceau whose textbook, first published in 1668, was used all over Europe.

Holland had at that time its great period of expansion and colonization. More than any other country it developed its waterways. Henrik van Deventer was a goldsmith who became a physician; being interested in mechanical problems, he entered the field of orthopedics. His wife was a midwife, and he became interested in the architecture and mechanics of the pelvis, a subject to which he made important contributions. It is not astonishing that this mechanical age produced the most important tool in obstetrics, the forceps. Invented by a barber surgeon Chamberlen, it was kept a family secret, was discovered independently by Jean Palfyn, and was approved by the Paris Academy in 1723.

The education of midwives was improved. In 1630 they were given regular courses in France at the Hôtel-Dieu. In Germany they were instructed by the municipal surgeons. Great names appear among the

midwives of the period, such as Louise Bourgeois, Marguerite du Tertre, and Justine Siegemundin. They were skilled obstetricians, and their books were widely read.

In the eighteenth century pathology became anatomic. From Vesalius on, pathologic changes had been observed in organs and such findings were collected by Théophile Bonet in his *Sepulchretum* of 1679. It was Morgagni, however, who in 1761 laid the foundation of modern pathologic anatomy and created the method of pathologic research that was to be followed from then on. In the third volume of his *De Sedibus et Causis Morborum* he discussed pathologic changes of the female genital organs. In the following years many dissertations were written on such subjects, and the method of Morgagni was continued by Bichat and Virchow who traced anatomic changes in the tissues and in the cell. On the basis of these studies the various gynecologic diseases could be sharply defined, and most disease entities that we recognize today were established during the nineteenth century in pursuit of this trend.

As soon as pathologic anatomy was established, a new task was set for clinical diagnostic. Its purpose became to recognize anatomic changes on the living organism with physical methods. This is why percussion and auscultation were introduced at that time and became chief methods of physical diagnostic. It was Lejumeau de Kergaradec who had the brilliant idea of applying Laennec's auscultation to watch the heartbeat of the fetus.

The eighteenth century was an international century. Every country made its contribution to gynecology. In England William Smellie and William Hunter produced their superb atlases of the pregnant uterus. Special lying-in hospitals were erected in every country. They not only improved the conditions of women in childbirth, but improved also the educational facilities for midwives.

In the nineteenth century therapy became anatomic, and this explains the tremendous development of surgery. General anesthesia, antisepsis, and asepsis broke the age-old bonds that had impeded the progress of surgery. Anesthesia and asepsis were found because medicine had reached the point at which surgery was no longer the ultimum refugium to which resort was taken when all other methods had failed, but had become a primary goal. Surgery revolutionized gynecology and obstetrics. Major abdominal operations could be performed now. Large tumors could be removed without danger to the patient, and cesarean section was no longer an act of desperation. The development of surgery also created a new type of hospital, and the number of deliveries that took place in hospitals increased considerably. In this great development American surgeons have played a very important part, and I need only remind you of the names of Ephraim McDowell and James Marion Sims.

Today a cycle has come to an end. The anatomic approach inaugurated in the Renaissance has been applied to one medical field after another, and today we are in a physiologic era. Physiology is in the foreground of all considerations. We no longer operate for a retroflexion merely because the uterus does not hold the position prescribed for it by the textbooks. Function is being considered first of all. New physiologic discoveries, particularly that of hormones and vitamins have stimulated both gynecology and obstetrics.

I cannot discuss the recent developments, and I need not do it because the gynecology that you practice today represents the experience of the

last fifty years. I would like to draw your attention, however, to the social history of the period, an aspect that has been frequently underestimated.

The Industrial Revolution was the event that had the most profound influence on the entire nineteenth century and on our days too. Industrialization created employment not only for men but also for women and children. Women entered the process of production in increasing numbers. The textile industries were built up almost entirely with women labor, but women worked also in mines underground and in other industries until factory legislation stopped some of the worse abuses. As a result, health conditions deteriorated, particularly among women. The population increased, especially the indigent population that lived crowded in slums, in the suburbs of cities, under atrocious hygienic conditions. We often forget that at the time when the French clinic flourished and modern medicine was making tremendous progress, health conditions were exceedingly bad. The reports of Villermé in France, of 1840, and of Chadwick in England, of 1842, speak an eloquent language.

Industrialization had other results. Women were doing men's work. The development of industry would have been impossible without them. It was nothing but justice that they should have been entitled to share not only man's labor but also his rights, that they should have had equal opportunities of education and that the professions should be open to them. It was felt that they should have a voice in the administration of the commonwealth. A long struggle ensued against the vested interests of men, a struggle that was not without dramatic episodes. Women won their case in most civilized countries, at least to a certain extent. Their gains are now challenged in the Fascist countries.

This whole development had some definite bearing on gynecology. Woman may have equal rights and all occupations may be open to her. Modern society needs her labor, but nevertheless she remains woman and carries the additional burden of her sex. She creates commodities and services, but she creates, in addition, our children. She is therefore entitled to added protection. She cannot be considered free and equal as long as pregnancy means loss of a job. If she is to be truly free and equal, she must be guaranteed regular vacations on full pay and the rest she needs during pregnancy and after childbirth without loss of wages. Maternity homes, nurseries, and all other means for the protection and restoration of health must be made easily available to her.

The strain of life in an industrial society weighs heavily on the working girl and woman, and maladjustments of some kind or another make them seek the advice of a gynecologist. My colleague Sellheim in Leipzig used to say that a woman's period is like a clock. Whenever something goes wrong in that complicated mechanism, the clock immediately reveals it by being fast or slow or otherwise wrong. Gynecologic complaints drive a woman to the physician, but her ailment may not necessarily be the result of a gynecologic disease. A psychologic or social maladjustment may be responsible for it. A gynecologist who would be nothing but a surgeon would be utterly helpless in such a case.

Gynecology, as the word indicates, is the science of woman in health and disease, of her physiologic and pathologic processes and of all problems peculiar to her. This requires that the gynecologist be not only a scientist but also have a broad psychologic and social approach to his problems.

I have shown you that the gynecologist had two ancestors. The surgeon was his father, the midwife his mother. From the father he inherited techniques, knowledge, and skills; from the mother he received in addition the human touch. Like the midwife of old, he must be the confidant of women who consult him whenever they are in trouble, whether their ailments are organic or not.

In gynecology and obstetrics as in every other field of medicine, the urgent problem of our day is to make whatever knowledge we have available to all who need it. Great progress has been achieved and many human lives are being saved that would have been lost irrevocably only yesterday. But we all know that conditions could be better than they are. In spite of all progress, with all the knowledge and equipment we possess, we still lose in this country annually about 9,000 young mothers from the results of pregnancy and childbirth, and we lose many of them needlessly. Every year more than 180,000 young women go through the trying period of pregnancy and childbirth and the result is a dead child or one that will die during his first year of life. Our task is not yet solved. Science and technology developed more than ever before. As a result medicine progressed, the structure of society changed, and so did the position of women in it. Conditions are totally different today from what they were one hundred or only fifty years ago. It is obvious that adjustments must be made.

You as individuals and as a group are leaders in your field. Through your researches you have advanced the science of gynecology considerably. Your society was founded in 1876 and when you look back you can be justly proud of your achievements, but you must remember that since 1876 the world has changed a great deal. New social problems have become very acute, and I am sure that in this field also the country is looking to you for leadership.

Editorials

Depriving the Infant of Its Placental Blood

WHETHER the time of clamping the umbilical cord is of significance to the baby has been a controversial subject for many years. Older workers advocated late ligation in the belief that the greater amount of blood flowing to the baby was beneficial and the initial weight loss of the infant was less than after late clamping. Recently early clamping has been practiced by those who advocate the use of placental blood for "blood bank" purposes but, even when the blood is not collected, the practice is a common one.

The amount of blood in the placenta is large, averaging over 100 c.c.* In occasional instances it is over 200 c.c. About 50 per cent of this blood flows into the baby in the first minute after delivery and over 90 per cent in the first ten minutes. Since the average blood volume for newborn infants is about 500 c.c., it is apparent that the placenta is capable of raising the blood volume by about 20 per cent. It is of some interest to note that blood continues to enter the infant's circulation after pulsation of the cord has ceased.

Recently DeMarsh, Alt, Windle and Hillis† undertook a study of the effect of early clamping of the cord on the red corpuscle count and the hemoglobin content of the blood during the first week of life. They found that, in the group where the cords were ligated early, the red corpuscle count and the hemoglobin were, on the average, lower than in infants whose cords were clamped after the placentas had separated. The reticulocytes showed a higher average value when early ligation was practiced, suggesting a greater demand for blood in this group than where clamping was delayed.

These authors point out that the placental blood normally belongs to the infant and that its deprivation amounts to the equivalent of a rather severe hemorrhage. The loss of blood may be a serious matter for the prematurely born infant, but even in the full-term infant the blood received from the placenta may be an important source of iron for the manufacture of hemoglobin later on. During the physiologic anemia which develops in the first two to three months of life, hemoglobin is broken down, liberating iron. This iron is not lost from the body but is stored in the tissues and is used in the synthesis of hemoglobin as needed. It is quite possible that loss of placental blood is a factor predisposing to anemia during later infancy.

The study of DeMarsh, Alt, Windle and Hillis offers convincing evidence in favor of late clamping of the cord. The use of placental blood for blood bank purposes hardly justifies interference with a physiologic process.

HARRY BAKWIN, M.D.

Haselhorst, G., and Allmeling, A.:* Ztschr. f. Geburtsh. u, Gynäk. **98: 103, 1930.

†*DeMarsh, Q. B., Alt, H. L., Windle, W. F., and Hillis, D. S.:* The Effect of Depriving the Infant of its Placental Blood, J. A. M. A. **116**: 2568, 1941.

Second American Congress of Obstetrics and Gynecology

IN RESPONSE to a country-wide demand, a second Congress devoted to this important field of medicine will be held in St. Louis on April 6 to 10, 1942. The success of the previous gathering in Cleveland in 1939 may be measured by the attendance of several thousand persons, including physicians, nurses, public health workers, and hospital administrators. The program of the previous Congress embraced features appealing to each and all of these varied groups and that being prepared for the coming one will be equally catholic in its presentation.

The good health and welfare of womankind constitutes an outstanding asset in every nation and all effort should be made to preserve her important functions. This country has been held up in the past as irresponsive in this respect, whether justly or unjustly. It may be stated, however, that within recent years great and noteworthy progress has been demonstrated, as is evidenced by the lowered mortality and morbidity rates associated with childbearing and the reduction of neonatal and early infancy deaths, throughout almost all parts of the United States.

There are still many problems to be solved, medical, economic and social, and much more can be accomplished through the medium of congresses such as this and the opportunities thus afforded for the discussion and dissemination of ideas and proposals for further advancements in this field.

Future issues of the JOURNAL will present additional details of the program and other information relative to this important gathering.

Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

Review of New Books*

Gynecology and Obstetrics

A second edition of Martius' *Gynecological Operations*[1] has appeared after an interval of four years. The first edition was most favorably commented upon in these reviews. Likewise the comment on the English translation, prepared by Dorland, was favorable.

The new edition contains several additional operations: The extended vaginal hysterectomy after Schauta-Stoeckel, as practiced in Vienna, is very clearly and simply depicted and described. Partial colpoclysis, according to Labhardt, by reduction of the vaginal canal to pencil diameter and building up of a perineum almost to the urethra, applied to old women who are poor operative risks, under local anesthesia, is described. Cottes' presacral sympathectomy has also been added. In addition to the new illustrations which illuminate the newly described operations, additional anatomical drawings of the female pelvic organs have been added. As mentioned in reviewing the first edition, the illustrations are particularly praiseworthy because of their simplification and schematization without loss of clearness and merit. The brief but incisive text is admirable in its clarity. This book has a wide scope.

ROBERT T. FRANK.

In this concise presentation *Essentials of Gynecology*[2] Brady and Kurtz have augmented a series of lectures on gynecology to nurses and have added a considerable amount of nursing procedures. Such a clear and concise presentation should form an excellent textbook not only for nurses and the preclinical medical student as well as a means of quick review for physicians preparing for hospital or State Board examinations. The division of the material is excellent, and the illustrations borrowed from many standard texts have been well chosen to correlate the descriptive text. There is a very fine chapter on female urology. The authors state that the interposition operation is preferred for complete prolapse of the uterus at both teaching institutions in Baltimore.

PHILIP F. WILLIAMS.

*NOTE: The Department of Book Reviews will appear, in future, at regular intervals, namely in January, May, and September.

The present offering contains few items because a large number of reviews appeared recently. Books for review should be forwarded to Dr. Hugo Ehrenfest, 3720 Washington Blvd., St. Louis, Mo., at least two months in advance of the above dates.

R. T. F.

[1]**Die Gynaekologischen Operationen.** Von Professor Dr. Heinrich Martius, Direktor der Universitaets-Frauenklinik in Goettingen. Zweite verbesserte Auflage, 424 Seiten, mit 427, zum groessten Teil farbigen Abbildungen und Bilderreihen von Kaethe Droysen, Verlag von Georg Thieme, Leipzig, 1941.

[2]**Essentials of Gynecology.** By Leo Brady, Assistant Professor of Gynecology, University of Maryland, etc., and Ethna Louise Kurtz, R.N., Head Nurse, Brady Urologic Institute, Johns Hopkins Hospital, etc. 57 illustrations, 251 pages. The Macmillan Co., New York, 1941.

This important text *The Heart in Pregnancy and the Child-Bearing Age*[3] by Hamilton and Thomson may be regarded as a logical outcome of the Cardiac Clinic in the Boston Lying-In Hospital. This clinic established years ago has continuously expressed its experiences in current literature. Here the entire subject is gathered together and offered to the physician interested either in cardiology or in obstetrics.

The first section of the book opens with a general discussion of heart disease and continues with the treatment of the cardiac woman who becomes pregnant. Dr. Frederick C. Irving, Obstetric Chief of the Boston Lying-in Hospital, has written a section dealing with the delivery and obstetric aftercare of cardiac patients who have become pregnant. The new policy of this hospital regarding such patients, to subject fewer women to abdominal hysterotomy and to salvage more babies, has resulted in a lowering of the maternal mortality rate from 6.4 per cent to 2.6 per cent, and there has been but one death from heart failure compared to eight in the first series. Irving regards ether, carefully and properly given, to be the safest anesthetic in these cases, yet he does not feel that heart disease or failure per se contraindicates spinal anesthesia. Although in some reported series the majority of deaths of women with rheumatic disease who are pregnant occurred in the first twenty-four hours after delivery, the authors state "that congestive heart failure rarely occurs or re-appears following delivery at term." Circulatory burden is thoroughly discussed, many electrocardiographic tracings and x-rays of the heart are introduced to support the conclusions regarding the work of the heart during pregnancy.

The physiology of the normal and of the diseased heart in pregnancy are well contrasted. The authors regard the circulatory load in pregnancy to have reached the maximum before the ninth lunar month and note a decrease during the final weeks, tenth lunar month, of pregnancy. So far as the complications of pregnancy which are accompanied by renal or vascular lesions, generally grouped under term toxemias, are concerned, these abnormal manifestations are dealt with separately and at length. The authors do not regard eclampsia and pre-eclampsia as tending to be commonly followed by chronic heart disease, heart failure, or significant acute myocarditis. In discussing heart disease in young women, the authors state that the recurrence in rheumatic fever is very rare in the pregnant woman and in the puerperium, but may occur occasionally in girls under twenty-three years of age. There are chapters on neurocirculatory asthenia and bacterial endocarditis as well as other infrequently seen cardiac lesions in the childbearing age. The book is an outstanding contribution to obstetric literature.

PHILIP F. WILLIAMS.

In 1932 and 1935 Bernhard Zondek, in a monograph *Hormone des Ovariums und des Hypophysenvorderlappens*, reported his voluminous and fundamental researches dealing with the sex hormones. The present monograph[4] covers his work accomplished since then and including 1940, mainly carried out in Jerusalem.

The wide activities of this investigator and clinician embrace all of the sex hormones: pituitary, androgens, and estrogens as well as some of the other endocrine glands, both from an experimental and clinical standpoint.

The subjects covered include the occurrence of some estrogenic substances in nature; experimental and clinical investigations on the percutaneous use of estrogens and androgens; the effect of protracted treatment with high doses of estrogen; the fate of the sex hormones in the organisms; clinical investigations of the cycle of the female organism, and the mechanism of menstruation. Of particular interest is the inhibition of the pituitary function by estrogens which has been analyzed, inclusive of the gonadotropic, thyrotropic and parathyrotropic, and adrenotropic

[3]**The Heart in Pregnancy and the Childbearing Age.** By Burton E. Hamilton, M.D., Cardiologist to the Boston Lying-in Hospital, and K. Jefferson Thomson, M.D., Associate Physician, Metropolitan Life Insurance Company Sanatorium, etc. With a section: Delivery and Obstetrical After-Care of Cardiacs, by Frederick C. Irving, Professor of Obstetrics, Harvard Medical School, etc. 402 pages. Little, Brown and Company, Boston, 1941.

[4]**Clinical and Experimental Investigations of the Genital Functions and Their Hormonal Regulations.** By Bernhard Zondek. 264 pages. The Williams & Wilkins Company, Baltimore, 1941.

hormones. The estrogens do not react alike on these various functions. Of great importance are the investigations dealing with the production of uterine hemorrhage in animals below the primates, by means of gonadal and estrogenic hormones.

ROBERT T. FRANK.

This short brochure, *Female Sex Hormones*,[5] contains four articles on the sex hormones, presented at the Bicentennial of the University of Pennsylvania. The first, by Doisy, gives a clear description of the chemistry and physiology of "The Ovarian Follicular Hormone." Philip E. Smith presents the "Gonadotropic Hormones" and offers the evidence for and against there being two such hormones, one follicle stimulating and the other luteinizing.

R. T. Frank takes up the "Hormonal Blood and Urine Status," estrogenic, androgenic, progestational and gonadotropic, in the various conditions of health and disease. Elmer L. Sevringhaus concludes with a description of the "Sex Hormone Therapy in the Female."

ROBERT T. FRANK.

Spermatozoa and Sterility,[6] a clinical manual by Weisman, is addressed to gynecologists and urologists as well as general practitioners. It covers every aspect of the subject, even such an unnecessary one as a description of pregnancy tests. The anatomy, the physiology, and the chemistry of the spermatozoa are taken up. Minute techniques necessary for the study of sperma in the male and recovery in the female are described. The causes and the treatment of male sterility, the sperma in cryptorchidism, artificial impregnation and its legal aspects, are some of the subjects covered.

As every aspect of sperma and its implications are contained within the covers of this monograph, it is a valuable source book. The text is clear, concise, and well documented.

ROBERT T. FRANK.

Miscellaneous

Gilbert Applehof, Jr., offers a valuable contribution to the study of the total structure of marriage,[7] namely the viewpoint of the minister. Rev. Applehof has been counseling couples on marriage for a great many years, both in the marriage clinic and in the rectory. The material in his book proceeds chronologically from adolescence, through the wedding and honeymoon, to the problems which arise later in marriage. He offers an interesting pre-marital questionnaire to be filled out by both partners which includes actual biographical data and attitudes toward such things as: finances, emotional adjustment, attitudes toward home and marriage, religious and sex instruction and attitudes, health, social adjustment, and understanding of marriage problems. Although the questionnaire is limited, it should give the counselor a good idea of the situation. Despite the many merits of this book, which is filled with universally important information, it is a marriage manual for the naive and religious couple, and in this capacity a truly excellent and inspiring guide, but the more sophisticated group, while learning a great deal, might not be willing to accept the continual combination of complete frankness and openness mingled with the stress on the religious aspect of the subject. Rev. Applehof portrays the sexual aspects of marriage without reserve, and yet on the next page will remind you that marriages are made in heaven.

YVONNE DEP. FRANK.

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[5] **Female Sex Hormones.** By Edward A. Doisy, Philip E. Smith, Robert T. Frank, and Elmer L. Sevringhaus. 58 pages. University of Pennsylvania Press, Philadelphia, 1941.

[6] **Spermatozoa and Sterility.** By Abner I. Weisman, M.D., Adjunct Gynecologist, Jewish Memorial Hospital, N. Y., etc. With a Foreword by Robert L. Dickinson. 314 pages, 77 illustrations. Paul B. Hoeber, Inc., New York, 1941.

[7] **You Can Be Happily Married.** By Gilbert Applehof, Jr., Rector of St. John's Church, Alma, Mich. 218 pages. The Macmillan Company, New York, 1941.

The third volume of *The Therapeutics of Internal Diseases*[8] edited by George Blumer, is devoted to the infectious diseases as well as the various types of parasitisms. The book also takes up dehydration, edema, acidosis, metabolism, and the endocrine organs. While the first few sections are of little interest to the obstetrician, we find Martland giving a good discussion of asphyxia which should be of interest to the obstetrician.

The discussion of edema and dehydration is pertinent to the care of pregnant women, and the treatment of various toxemic conditions. McIvor in a well-written chapter on Pre- and Post-Operative Treatment has outlined the preparation for operation of patients with special diseases, all of which are common in gynecologic practice.

Under the section on Heart Diseases and Heart Failure there are two excellent sections on the heart in anesthesia and the general subject of marriage and pregnancy.

PHILIP F. WILLIAMS.

Cleckley in *The Mask of Sanity*[9] has selected those psychopathic personalities who do not fit into the community, and yet today, in the eyes of the law, are pronounced sane. They are serious problems for their relatives, the police, juries, and courts because in law, they are held responsible for their conduct. The author has seen a large number in the veteran hospitals. In these hospitals they form a serious problem as they cannot draw compensation.

These patients have no delusions, hallucinations, or signs of psychosis or psychoneurosis. They may commit crimes, such as forgery and bigamy, for which they are arrested. They take part in brawls, drunkenness, wife beating, and similar less serious disturbances. In spite of promises, they relapse again and again. Some, who show no real criminal tendencies, take drugs. To avoid the consequences of their misdeeds, they voluntarily seek hospitals as a temporary refuge and as an expedient to escape legal consequences. They soon weary of their confinement and insist upon being released. The hospital authorities are helpless because they cannot legally commit them, because of their being sane in the eyes of the law. Therefore they are again set at liberty. Among these individuals one finds business men, lawyers, physicians; among the nine case histories that he gives in detail, the author describes a well-known but unidentified psychiatrist. In this well and interestingly written monograph, the author pleads that some provision be made in law and in medicine to study and give adequate control and care for these patients.

ROBERT T. FRANK.

Gesell[10] has attempted the difficult task of reconstructing the life of Kamala, the wolf girl, from the diary placed at his disposal by the Reverend J. A. L. Singh in whose orphanage Kamala spent the nine years of her human association. She lived approximately eight years with her wolf foster mother and died at the age of seventeen years at the orphanage. It took fully two years to wean her from her wolpine ways. She never attained complete adjustment. The other child, Amala, lived for even a shorter period among humankind.

Dr. Gesell's interpretations are ingenious and interesting but far from convincing. This applies particularly to his attempted visualization of Kamala's wolf life which, to me, resembles a weak and emasculate imitation of Mowgli in Kipling's

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[8] **The Therapeutics of Internal Diseases.** Volume III. Supervising Editor George Blumer, Clinical Professor of Medicine, Yale University School of Medicine, etc., and Associate Editor Albert J. Sullivan, Adjunct Clinical Professor of Medicine, George Washington and Georgetown Medical Schools, etc. D. Appleton-Century Company, Inc., New York, 1941.

[9] **The Mask of Sanity.** By Hervey Cleckley, Professor of Neuropsychiatry, University of Georgia School of Medicine. The C. V. Mosby Company, St. Louis, 1941.

[10] **Wolf Child and Human Child,** being a narrative interpretation of the life history of Kamala, the wolf girl. By Arnold Gesell, M.D., Director of Yale University Clinic of Child Development. Illustrated with photographs and drawings, 107 pages. Harper and Brothers, New York, 1941.

Jungle Book. More successful is the analysis of her life in the orphanage from which a number of important physiologic observations have been gleaned. Numerous photographs taken by Dr. Singh add interest to this unique biography.

ROBERT T. FRANK.

Griffith and Mitchell have revised their book on *Disease of Infants and Children* with a new title *Textbook of Pediatrics.*[11] The influence of the entire pediatric group is reflected in the long list of names of those who have contributed to or assisted in the preparation of the book. The text brings in line the most recent advances and modern ideas in the treatment of the diseases of children. The authors have been particularly generous in the development of those conditions in which the obstetrician would be interested either directly at the time of delivery or in the immediately postnatal period. They have devoted some forty pages to the disease of the newborn infant, not only from the standpoint of prematurity and immaturity but as well from the standpoint of infections and general conditions. The chapter on breast feeding and artificial feeding in the first year of life discusses the nutritional problems the obstetrician who continues care of the child will have to handle. One feels that this should be an excellent volume to have at hand in the Maternity Division of any hospital.

PHILIP F. WILLIAMS.

Dr. Mary McKibbin-Harper in the new book *The Doctor Takes a Holiday*[12] has brought together some interesting sketches of her travels in the Far East. Already well known for her previous travel books, Dr. McKibbin-Harper lays before one not only the tourist sights of the Near East and Orient but carries one through the various phases of medical practice in those lands. This unusual combination of travel lore, sociology, and medicine in foreign parts makes the book one which once begun is not easily laid down.

PHILIP F. WILLIAMS.

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[11]**Textbook of Pediatrics.** By J. P. Crozer Griffith, Emeritus Professor of Pediatrics in the University of Pennsylvania, etc., and A. Graeme Mitchell, Professor of Pediatrics, College of Medicine, University of Cincinnati, etc. Third edition, revised and reset, 220 illustrations, 991 pages. W. B. Saunders Company, Philadelphia, 1941.

[12]**The Doctor Takes a Holiday.** By Mary McKibbin-Harper, M.D. Illustrated, 349 pages. The Torch Press, Cedar Rapids, Iowa, 1941.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Menstruation

Ashley-Montagu, M. F.: Physiology and the Origins of the Menstrual Prohibitions, Quart. Rev. Biol. **15**: 211, 1940.

In a very concise article Ashley-Montagu here repeats the effort, often made before, to find in the results of recent scientific investigations a basis for an acceptable explanation of the old and still widely persisting belief that "the female during her catamenia is considered to be herself unclean and as noxious as the effluvium itself."

Folkloristic and related aspects of this question are quoted from the well-known works of Briffault, Havelock Ellis, Frazer, Ploss and others. Next are given brief quotations from a very large number of recent studies, experimental, psychologic and particularly chemic, and their results are critically analyzed. The thoroughness of the writer's efforts are proved, e.g., by his discovery that many beauticians now advise against a permanent hair wave during the period, because it will not take as well. He feels that there might be a modicum of truth in this assertion because "it is well known that the bioelectrical potential of the body differs from the normal during menstruation, as recently shown by Burr and Musselman." In this connection, however, he overlooks the fact that this momentary change in the electrical potential occurs only at the moment of rupture of the ripe follicle, i.e., some time before the start of the flow. It also seems surprising that the writer fails to mention the established and significant role played by menstrual blood in the causation of definite allergic phenomena.

In summarizing his studies, the author states that menstruous women apparently are capable of exerting noxious effects upon living tissues and that the responsible agent seems to be an alkylamine, probably thimethylamine. He concludes that it still is impossible to establish the possible physiologic origin of the various menstrual prohibitions.

HUGO EHRENFEST.

Cañizares, R.: The Utero-Ovarian Cycle in the Cuban Woman, Rev. cubana de obst. y ginec. **2**: 105, 1940.

In a study of 200 white, negro, and mestizo women, the author developed several statistical conclusions which are interesting in comparison with common findings in the climate of the United States. The menarche varied between the ages of 12 and 15. Most white women had their menstrual onset at 14 years, the negro at 12, and the mestizoes showed two distinct groups commencing at the ages of 12 and 15.

In the group as a whole a normal menarche was reported for 58 per cent; dysmenorrhea in 31 per cent. A marked regularity in menstruation was noted: the negro most regular; white women second. The most common menstrual formula was three days every twenty-eight days. The age of menopause in this group was 45 to 54 years and the incidence of sterility was only 6.8 per cent.

R. J. WEISSMAN.

Neufeld, N., and Boas, v. Emde: A Critical Review of the Cycloscope Method for the Diagnosis of Ovulation, J. Contraception 4: 99, 1939.

During the last few years, Samuels of Amsterdam has published a number of articles in different medical journals describing a new method for the determination of the time of ovulation. Samuels makes the assumption that the cellular gas metabolism in the tissues, or tissue respiration, is a measure of the hormonal processes in the human body, and he describes a simple instrument, which he calls the cycloscope, by means of which the reduction time of the oxyhemoglobin in the blood can be exactly measured.

Samuels thinks that by his reduction figures he has gained an insight into the hormonal processes which take place in the body of healthy and ill men and women, and he applies the spectroscope method extensively for diagnostic and therapeutic purposes. He thinks that after a short "provocative" treatment of the endocrine glands with short waves, he can diagnose all kinds of endocrine troubles and even state which of the glands is hyper- or hypofunctional. The diagnosis of tumors, the differential diagnosis of malignant and benign growths, of every early pregnancy, of impending abortion, etc., all this is a simple matter with this omnipotent instrument.

The spectroreductometer appears to be the same as the instrument of Drs. Dausset and Ferriers. The cycloscope is the same instrument as the French one, only somewhat simplified.

The instrument with which Norbert Neufeld and van Emde Boas made their tests was a spectroreductometer which is sold as Dr. Samuels' cycloscope.

As the authors have now judged the instrument to be faulty and the method to give no results to prove that there is repeated ovulation, they state that even if, with another instrument and another method, they could obtain a curve of the reduction time, it would be rash to draw conclusions that the reduction time is related to ovulation.

Dr. Samuels' proofs that ovulation takes place twice or three times a month are not conclusive. His foremost proofs are first, the results of the cycloscope, which the authors reject; and second, the published findings of laparotomies, which are very few and unconvincing. Various authors have often emphasized the fact that from inspection alone it is impossible to state with certainty how ripe the follicles are, or how old the corpus luteum is.

J. P. GREENHILL.

Palmer, R., and Devillers, J.: Ovarian Cycle and Temperature Curve. Utilization for the Diagnosis of the Date of Ovulation, Comp. rend. Soc. franç. de gynéc. 9: 60, 1939.

During the past year the authors have analyzed the temperature curves of women in whom the menstrual cycle was being studied. Rubinstein had shown that rectal temperatures taken between six and seven in the morning are at their minimum on the day of ovulation. Palmer and Devillers were also struck with the low temperatures observed at the beginning of the luteal phase of the cycle. They believe that whereas it is not permissible to maintain that one can predict the day of ovulation and the formation of a corpus luteum from the temperature curve, nevertheless when other signs and symptoms of ovulation are present, the temperature curve fixes the date of ovulation in a more precise manner than do the other signs. This information is important for three purposes. First to determine the period of fecundation. The beginning of this period is at the time of the second lowest temperature, the most favorable time is at the lowest temperature, and the entire period continues only forty-eight hours after the drop in temperature.

The second purpose is to be able to attribute to ovulation certain intermenstrual disturbances such as pain, bleeding, leucorrhea, breast symptoms, and general and psychic disturbances.

The third purpose is to determine the date of the following menstrual flow in women who have irregular cycles. This knowledge will eliminate the necessity for performing repeated biopsies of the endometrium to obtain a premenstrual endometrium.

J. P. GREENHILL.

Vollmann-Siebr, U.: Investigation of the Body Temperature of Women in Correlation With the Phases of the Genital Cycle, Monatschr. f. Geburtsh. u. Gynäk. **111:** 41 and 121, 1940.

The author recorded the daily rectal temperatures for 284 menstrual cycles in 37 women and found that there is a biphasic wave-like curve during each menstrual cycle. There is a decrease in temperature following the menses and a characteristic increase in the intermenstruum. Likewise, there is a rise in temperature in the premenstrual period and a sudden fall just before the onset of bleeding. Men, children, and women past the menopause do not show any cyclic fluctuations in the rectal morning temperature. During pregnancy the temperature is strikingly constant. During the amenorrhea associated with lactation, there are also no cyclic variations but just before the onset of the first menses after delivery, the temperature exhibits the biphasic curve again.

The author made use of the temperature curves to determine the length of the post- and premenstrual phases. He observed that the duration of the premenstrual phase is relatively independent of the menstrual cycle, whereas the postmenstrual phase varies directly with the length of the cycle.

J. P. GREENHILL.

Vollmann, R.: Statistical Analysis of the Phases of the Genital Cycle in Women by Using Intermenstrual Pain as the Criterion of Ovulation, Monatschr. f. Geburtsh. u. Gynäk. **110:** 137, 1940.

The symptomatology, etiology, and physiology of intermenstrual pain are discussed by Vollmann based on experimental research and a menstrual calendar record kept for three years by a patient. The author's hypothesis is that intermenstrual pain is similar to a viscerosensory reflex, the result of tubal spasms, determined by the menstrual cycle. In the opinion of the author, intermenstrual pain coincides with ovulation.

J. P. GREENHILL.

Croci, C.: The Cold Pressor Test During the Menstrual Cycle, Monatschr. f. Geburtsh. u. Gynäk. **110:** 334, 1940.

The author performed the cold pressor test on 18 women during various times in the menstrual cycle. In 14 cases he found a diminished response of the blood vessels at the time which corresponded to ovulation. He believes that the change in the reaction was an indication of impending ovulation.

J. P. GREENHILL.

Morton, Daniel G., and Hayden, Charles T.: Incidence of Ovulation as Determined by Endometrial Biopsy, West. J. Surg. **49:** 15, 1941.

The investigation of the endometrium in successive cycles in normally menstruating, healthy young women indicates that anovulatory cycles are rare, probably not more than one in ten up to the age of 40 years. With the approach of menopause, after 40, the incidence of anovulatory cycles increases markedly, about one in two. Thus, it appears that the presence of essentially regular menstruation can be interpreted almost uniformly as an incidence of normal, regular ovulation in women below 40.

These observations tend to minimize the importance of endometrial biopsy in sterility investigations in normally menstruating women.

HUGO EHRENFEST.

Netter, Albert: Anovulatory Menstruations, Presse méd. 48: 333, 1940.

The author reviews the known animal and human experimental endocrine facts relative to spontaneous and induced anovulatory menstruation. He concludes that the normal woman can have anovulatory menstrual periods from puberty to menopause. During the mature sexual period, the failure of ovulation is exceptional. Such a failure of ovulation does account for certain cases of sterility with or without functional bleeding. The treatment of these latter cases unfortunately is still very deceptive.

CLAIR E. FOLSOME.

Soskin, Samuel, Wachtel, Hans, and Hechter, Oscar: Prostigmine Methylsulfate for Delayed Menstruation, J. A. M. A. 114: 2090, 1940.

The authors feel that since there is evidence in favor of the fact that the specific proliferative effects of estrogen are due to the acetylcholine liberating properties of the hormone, there is some connection between the parasympathetic nervous system and menstrual phenomena. It is seemingly possible that cases of delayed menstruation now generally ascribed to temporary endocrine dysfunctions might occur despite normal hormone secretion and be due to abnormally decreased vascular responsiveness. An attempt was, therefore, made to treat these cases by pharmacologic rather than by endocrine means.

The preparation used was prostigmine methylsulfate (1-2,000), and this substance invariably precipitated the menstrual flow in cases of menstrual delay (nonpregnant). The average time that elapsed between the last injection and the beginning of the flow was twenty-eight hours. The longest interval was seventy-eight hours, and the shortest interval was four hours. One to three injections were given on successive mornings, and the amount given was usually 2 c.c. The prostigmine had no effect on cases of delayed menstruation due to pregnancy. This latter group of cases were all given 2 c.c. on three successive mornings. A suggestion is made that this test could be used as a test for pregnancy.

WILLIAM BERMAN.

Shute, E.: The Diagnosis and Treatment of the Common Disorders of Menstruation, J. Canad. M. A. 40: 38, 1939.

Shute emphasizes the importance of attempting to determine the endocrine disturbance associated with menstrual abnormalities before hormone therapy is instituted. He recommends as a practical procedure, the estimation of blood estrogenic hormone level from determination of its antiproteolytic power.

Endocrine menorrhagia is usually associated with excessive blood estrogen. Oligomenorrhea is usually due to the reverse. Amenorrhea may be associated with either high or low blood levels. It is essential to determine which state is present and to discover if cyclic variations are present. The amenorrhea at the menopause may show similar relationships.

Dysmenorrhea also may be associated with low blood estrogen levels as well as with excessive estrogenic secretion.

All of these conditions must be looked upon as symptoms and not as syndromes. They should never be treated empirically. Where low estrogenic values are present, substitution therapy with estradiol intramuscularly is recommended. In the presence of excessive estrogenic activity, the following antiestrogens are suggested arranged approximately in order of ascending price and effectiveness: thyroid extract, prolan preparations, wheat germ oil, progesterone.

CARL P. HUBER.

Snaith, Linton: Menorrhagia Due to Essential Thrombocytopenia, Lancet 2: 684, 1940.

The author reports the case of a woman 27 years old with severe menorrhagia of two and one-half years' duration. No local or hormonal cause for the bleeding was determined and thrombocytopenia was discovered. After conservative measures

had failed, a splenectomy was performed. Normal periods were present during the year following operation. Careful examination of the blood including platelet counts and estimates of bleeding time are emphasized in the investigation of menorrhagia where no local cause is found.

CARL P. HUBER.

Greenhill, J. P., and Freed, S. C.: The Mechanism and Treatment of Premenstrual Distress With Ammonium Chloride, Endocrinology 26: 529, 1940.

It is postulated that the symptoms which occur in many women, premenstrually, result from the increase in extracellular fluid following sodium ion retention in the various tissues of the body. Therapy with ammonium chloride for the purpose of removing the extracellular fluid thus formed, is effective in relieving the premenstrual distress or tension.

The treatment was uniformly successful. All the patients were definitely relieved and were highly gratified with the therapy. Gross edema did not occur in the patients who had previously demonstrated it. Distention of the abdomen, nausea, and migraine were absent or insignificant during the ammonium chloride therapy. The patients claimed that they were less irritable and not subject to the periodic emotional upsets. All patients stated that there was an improved sense of well-being.

J. THORNWELL WITHERSPOON.

Miller, Norman F.: Dysmenorrhea, Canad. M. A. J. 42: 349, 1940.

The best approach to the treatment of dysmenorrhea is through an understanding of the fundamental anatomy and physiology of the structures involved. The nerve supply to the uterus may be of importance, due to the relation between emotional disturbances and menstrual disorders and also because of pathologic changes present in the nerve fibers and ganglion cells themselves. Disturbances in the blood supply of the pelvic organs, particularly stasis, may play an important part in the causation of congestive dysmenorrhea. Endocrine imbalance which may be either insufficient corpus luteum hormone or decreased estrogenic stimulation is important. The author warns that malpositions of the uterus, fibroids, infections, and endometriosis may cause dysmenorrhea but more often they do not. He feels that surgical treatment of dysmenorrhea is seldom necessary and that presacral neurectomy should be a last resort.

Successful management depends upon a willingness to meet the challenge of dysmenorrhea as a medical problem, a good understanding of the subject, recognition that there may be overlapping of predisposing and causative factors. Treatment should have two objectives: (1) relief of pain and (2) the correction of the underlying cause.

CARL P. HUBER.

Wittkower, E., and Wilson, A. T. M.: Dysmenorrhoea and Sterility. Personality Studies, Brit. M. J. 2: 586, 1940.

From a survey of biographic studies on 87 patients with dysmenorrhea, sterility, or both, the author points out that these complaints usually are secondary to certain psychologic characteristics in the individual, which antedate the appearance of the symptoms.

The survey included 57 unselected patients with primary dysmenorrhea and 30 patients with sterility of some years' duration. Of these, 19 complained of both dysmenorrhea and sterility. The control group consisted of 30 primigravidas who had never had dysmenorrhea.

In considering the childhood characteristics, the reaction to the various phases of adolescence, and the adult personality of these individuals, the author found certain personality types predominantly associated with each of the complaints under consideration. There was noted an overlapping of these personality types in individuals complaining of both dysmenorrhea and sterility.

The author found that although the incidence and intensity of psychologic maladjustment in some adults is to some extent the result of their disorders, the majority of ailing patients show definite maladjustment from early childhood.

In conclusion, he suggests probable explanations for individuals of certain personality types developing complaints typical of that type.

FRED L. ADAIR AND W. H. PHILLIPS.

Geller, Fr. Chr.: Infection and the Menstrual Cycle, München. med. Wchnschr. 87: 1110, 1940.

Geller discusses the relationship of infections and the menstrual cycle stating that the onset of various infectious diseases, such as scarlet fever, diphtheria, angina, furunculosis, etc., is strikingly frequent during the premenstrual period and during the first days of the menstrual cycle and that if infectious disease is already present, very frequently, there are further elevations of temperature during these periods. This fact has been recognized in tuberculosis.

In latent focal infections (granuloma of teeth, follicular tonsillitis, etc.), premenstrual elevations of temperature also occur so that fever in the premenstrual period almost always indicates a focal infection somewhere in the body. The premenstrual phase (corpus luteum) causes an increased susceptibility to infection. This phenomenon can be explained only by a decrease of the nonspecific resistance of the human serum to bacteria. Immunobiologic examinations confirm the fact that premenstrual elevation of temperature during infection is most probably due to increased bacterial activity, resulting from lowered bactericidal properties of the serum. This rise in temperature may, of course, be due partly to increased absorption of bacterial toxins and cellular debris, caused by better blood supply during this period.

C. E. PROSHEK.

Le Doux, L. A.: Some Observations on the Influence of Toxemias Upon Menstruation, New Orleans M. & S. J. 91: 463, 1939.

Toxemias associated with acute infectious diseases affect menstruation adversely. The untoward effect will depend upon the severity as well as the duration of the infectious process. Suppurative infections appear to furnish the greatest percentage of ovarian impairment. Toxins appear to have a stimulative as well as a depressive effect upon the ovaries, depending in which phase of the cycle they become active. The harmful effects of toxins may be upon the circulating hormone, the follicle, or both.

With the possible exception of gonorrheal infection, these disturbances are functional and capable of correction. Not more than one or two months should elapse before instituting treatment. Only such patients as have been subjected to a severe or long-standing toxemia may become permanently disabled. These patients should not be left entirely to their own devices or to nature, but should be treated as promptly as possible. In considering therapy, the author emphasizes that the use of ovarian hormones plays only a part in it.

J. P. GREENHILL.

Mach, Rene S., and Meyrat, Gilbert: Recurrent Hemorrhagic Meningismus Following Ovulation Period, Presse méd. 48: 292, 1940.

The authors report an interesting case of recurrent hemorrhagic meningism following ovulation in a woman 31 years old. The patient gave a history of menarche at age of 17; irregular menses associated with migrainelike headaches, and moderate leucorrheal flow fifteen days before advent of her periods. A pregnancy at the age of 26 years temporarily removed these symptoms.

The patient was brought to the hospital with a typical syndrome of meningismus during her intermenstrual period. There were positive Kernig and Trousseau signs. Lumbar puncture revealed blood-tinged spinal fluid. In all, four lumbar punctures were done and findings similar to the first were recorded. Three ampoules of proluton

were given after the fourth spinal puncture. It had been found that corpus luteum extract given orally once during an earlier attack had given partial relief.

Following hypodermic use of proluton in the midcycle, the patient ceased to have headaches, vomiting, and photophobia.

The authors make no comment upon the case other than to review the facts.

CLAIR E. FOLSOME.

MacGregor, T. N.: Amenorrhoea: Its Aetiology and Treatment, Brit. M. J. 1: 717, 1938.

With the premise that disappointing response to treatment of amenorrhea with the endocrines is probably due to indiscriminate administration, 97 cases are presented which have been investigated as thoroughly as present-day methods permit. The importance of a complete history and the role of anorexia nervosa and psychic shock in the production of amenorrhea is brought out. X-ray of the sella turcica, basal metabolic rate, determination of sugar tolerance, and determination of the amount of gonadotropic and follicular hormone excreted in the urine serve as guides toward a more rational hormonal treatment.

Twenty out of 97 cases investigated showed the amenorrhea to be due to recognizable pathology in the pituitary, ovaries, or uterus and in a few cases to systemic disease. In 77 cases, although no obvious pathologic condition was observed, laboratory findings disclosed a disturbance of function, particularly in the ductless glands and concerned with the menstrual process. These cases are described as "functional."

In treatment of functional amenorrhea, anorexia nervosa was most difficult and was treated with combined systemic and psychologic methods, followed by gonadotropic hormone. Patients with low basal metabolic rates were given thyroid and those with obesity were treated by a strict antiobesity diet.

Thirty patients showing excess gonadotropic hormone in the urine were treated with estrogenic substances (estradiol benzoate). Twelve of them failed to respond to treatment. Sixteen responded irregularly. In 2 patients the menses became regular, and in one, remained regular for twelve months.

Three out of 4 patients treated with anterior pituitary gland extract showed no response, while in the fourth uterine bleeding was produced for five months. Of 16 patients treated with urine gonadotropic hormone only two responded satisfactorily. Thirty patients were treated with serum and urine gonadotropic hormone, with 10 responding satisfactorily.

It is concluded that although the estrogens are of value in a few cases of amenorrhea in many they are contraindicated, since they produce a further inhibition of an already underfunctioning hypophysis. The most useful preparation in treatment of those cases due to hypopituitary secretion seems to be serum gonadotropic hormone alone or combined with the urine gonadotropic hormone.

F. L. ADAIR AND T. G. GREADY.

Lövset, J.: Follicular Persistence, a Constitutional Malady With (Incomplete?) Dominant Inheritance, Monatschr. f. Geburtsh. u. Gynäk. **111:** 154, 1940.

The clinical picture of follicular persistence is described by Lövset as a condition where periods of amenorrhea alternate with periods of metrorrhagia. In most instances, there is relative or absolute sterility. No satisfactory explanation has been found to account for this condition. The author reports a series of 10 families, from each of which 1 or 2 patients had come for treatment of the disturbance. The author's series also includes 2 pairs of identical twins in whom the disease appeared at the same time, ran the same course, and in whom the findings in uterus and ovaries at operation were identical. In 7 families there was evidence of cases of follicular persistence among relatives on both the father's and mother's sides. Because of this, the author feels it is justifiable to assume the presence of a dominant hereditary factor.

J. P. GREENHILL.

Donald, H. R.: The Female Climacteric and the Menopause, Brit. M. J. 1: 727, 1938.

The importance of differentiation between the climacteric and menopause is discussed; the climacteric is a general female epoch characterized by certain changes in function which lack any uniformity and which show great variations in severity, while the menopause is merely a local disturbance or cessation of menses.

Cases are presented in which the menopause was accompanied by occasional mild phenomena as hot flushes while the onset of the wide assortment of nervous symptoms which characterize the climacteric was delayed for fifteen years or more.

The distinction between climacteric and menopause is emphasized to counteract the impression that indications for endocrine, particularly estrin therapy are limited to the short period which follows the cessation of menses.

F. L. Adair and T. G. Gready.

Rowlands, I. W., and Sharpey-Schafer, E. P.: Effect of Oestradiol Benzoate on the Amount of Gonadotrophin Found in the Pituitary Gland and Urine of Postmenopausal Women, Brit. M. J. 1: 205, 1940.

Five women in the postmenopausal period suffering from incurable diseases were given intramuscular estradiol benzoate for varying periods before death. The anterior pituitary glands were removed at autopsy and were dried and weighed. Their potency was tested by preparing an extract and injecting hypophysectomized rats. These were controlled by five similar but untreated women.

The estradiol benzoate administration did not change the weight of the pituitary glands, but did decrease the amount of gonadotrophic substance. Microscopic studies of the rat ovaries showed that both hormones of the gonadotrophic complex were equally depressed.

The authors feel that this experiment shows the inhibitory effect of estradiol benzoate on the gonadotrophic activity of the anterior pituitary. They admit, however, that it might be due to increased pituitary activity which empties the gland of its hormone.

Fred L. Adair and George Bohlender.

O'Donovan, D. K.: Stilboestrol in Menopausal Therapy, Irish J. M. Sc. p. 159, April, 1940.

Stilboestrol (neo-oestranol 1) has an important role in menopausal therapy. It is effectively assimilated when given orally, and its reasonable price means that estrogenic treatment can be provided for hospital patients. In general, its mild toxic symptoms are not sufficient to outweigh the beneficial results obtained with it. Pending further experimental investigation, it is not considered advisable, nor is it usually necessary, to use it in any individual case for more than three months without interval. It is not considered a very successful therapy for the surgery menopause.

William C. Henske.

Bloch-Michel, H., and Prin, A.: Menopause and the Mitral Cardiopathies. The Cardiac Accidents of the Menopause, Ann. d'endocrinol. 1: 257, 1939.

The authors have followed 8 cases of mitral lesions in each of whom the advent of menopause seemed to be more than just an incidental factor in cardiac decompensation. They contend that the menopause represents for women with mitral lesions a time fully as dangerous as that in puerperal stages. The cardiac accidents of the menopause are serious. They may appear in the premenopausal period or some months following the cessation of menses.

The cardiac accidents of the menopause are characterized by the frequent association of common asystoles, vasomotor findings (Raynaud's syndrome), hemiplegia, convulsive crises, etc.

The cardiac accidents do not appear to be induced by the climacteric mechanical difficulties in the circulation balance. Neither the arterial or venous blood pressures nor the blood volume are sufficiently increased to make them explanatory of the menopausal asystoles.

The cardiac accidents of the menopause appear to be essentially based upon the neurovegetative imbalance and the cardiac and vasomotor disturbances which accompany the climatericum.

The prognosis of the menopausal cardiac accidents is very poor. The association of cardiac and endocrine therapy seems of but little value. Nevertheless this question of combining the treatments warrants more studies.

The endocrine therapy would probably be more favorable were it used prior to the cardiac decompensation period. Treatment of the cardiac accident of the menopause should be preventive.

CLAIR E. FOLSOME.

Hall, Francis C.: Menopause Arthralgia, New England J. Med. **219:** 1015, 1938.

The thesis of a specific menopause arthritis is supported by many writers. From a thorough study of 71 patients, Hall concludes that in many of these patients there does not exist a true arthritis, and for this reason he prefers the term menopause arthralgia. In this latter group the joint pain is found associated with other symptoms ascribable to ovarian deficiency. There were 53 patients suffering from arthralgia. Of 40, adequately treated with estrogenic material, 80 per cent were materially relieved of the menopausal and joint symptoms.

HUGO EHRENFEST.

Correspondence

The Colostrum Skin Test for the Diagnosis of Pregnancy

To the Editor:

Drs. Falls, Freda and Cohen presented a paper entitled "A Skin Test for the Diagnosis of Pregnancy" in March, 1941, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY. Their test involved the use of a solution of colostrum, and they intimated that this secretion might contain certain specific proteins or a protein-like substance which when injected intradermally would produce a difference in allergic response between pregnant and nonpregnant individuals.

The special solution of colostrum which they utilized was obtained and prepared under definitely standardized conditions. The technique of administering the intradermal injections was specific and outlined in detail. They interpreted the end reactions of the injections definitively, and considered the patient to be pregnant if only a slight reaction or no reaction ensued. Only when a marked allergic response manifested itself, did they consider the patient as nonpregnant. For details concerning their exact technique and procedure, one may refer to the original publication (AM. J. OBST. & GYNEC. 41: 431, 1941).

Falls, Freda, and Cohen presented the results of tests performed on 265 known pregnant women and 163 women who were definitely not pregnant nor post partum. They claimed that in the tests done on known pregnant women only "five false reactions" were obtained. Of the tests performed on the 163 nonpregnant women, it was stated that "typical nonpregnancy reactions were obtained in all but four patients, in whom typical pregnancy reactions were obtained which would have led to an incorrect diagnosis if the test alone had been relied upon."

From their results, it is evident that the authors were able to diagnose correctly pregnancy in 265 cases with an accuracy of 98.1 per cent. Of the 163 women who were not pregnant, they were able to say that 97.55 per cent of them were not pregnant. Owing to these excellent findings, Falls and his colleagues were quite sanguine regarding the diagnostic value of their test, and they therefore concluded their paper with the following remarks: "If our results are con-

firmed by others it will make the diagnosis of early pregnancy much simpler, quicker and more economical than the methods we now have at our command.''

The extreme simplicity of this method of testing and the excellent results obtained prompted us to attempt to corroborate their findings. Accordingly, colostrum was collected and prepared in exactly the manner advocated by these investigators. Their technique of injection and method of reading the reactions were closely followed.

Our series consisted of 150 women, of whom 100 were definitely pregnant and 50 definitely not pregnant. The 100 definitely known pregnant cases were white women from the obstetric out-patient department of the Metropolitan Hospital who were carefully selected so that they were between five and eight months pregnant. All these patients ''felt life'' and the fetal parts were palpable by abdominal examination in every case. The 50 nonpregnant women were nurses and patients from our hospitals who were regularly menstruating and who had no reason to believe that they were in a pregnant condition.

Results.—Of the 100 definitely known pregnant women, 48 per cent gave no allergic reaction whatsoever, 27 per cent gave evidence of some slight reaction, which we, according to the Falls' method, classed as ''weak reactions,'' while 25 pregnant women gave strong full-blown allergic skin reactions from the intradermal colostrum solution. The ''weak reactions,'' as suggested by Falls, were grouped together with the cases which did not react, and an analysis of the figures revealed that 75 per cent of the pregnant women reacted as Falls and his associates had predicted. However, there was an error of 25 per cent in these attempts to diagnose pregnancy correctly.

Of the 50 nonpregnant women who were regularly menstruating, 31 (62 per cent) gave strong allergic responses to the injections which was indicative, according to Falls and others, of the state of nonpregnancy. However, 13 women did not react at all to the injections and 6 reacted very slightly. This meant that 19 out of 50 cases gave false reactions which is an error of 38 per cent in attempting to diagnose the state of nonpregnancy by this test.

After having performed 150 colostrum intradermal tests for pregnancy with a percentage error of over 29 per cent, it was not considered feasible to continue with any further testing, in view of the relative inaccuracy of the test. Aside from the large error which we obtained when using the exact same technique employed by Falls, Freda, and Cohen, there are many other drawbacks in using an allergic skin reaction for pregnancy testing. The woman who is markedly allergic to any foreign protein, the interference from endocrine and metabolic dysfunctions, the necessity of a thorough knowledge of the fundamentals of wheal formation, the personal error in interpreting reactions and the variation in the chemical constituents of colostrum in different source individuals, all tend to make this allergic skin test of dubious value, at least for the present, as an aid in the diagnosis of pregnancy.

Perhaps with further study and standardization, this test can be made useful for the average practitioner, but until then, the profession should be cautioned against basing any diagnosis of pregnancy solely upon the use of the colostrum test for pregnancy. We feel that this test, because of the high degree of inaccuracy in the hands of those other than the original workers, may be placed in the same category as two earlier intradermal skin tests for pregnancy, the Gruskin test (Am. J. Surg. 31: 59, 1936) and the Gilfillen and Gregg intradermal test (Am. J. Obst. & Gynec. 32: 498, 1936). The former employed the use of a specially prepared placental protein substance, while the latter test involved the injection of antuitrin-S as a means of diagnosing pregnancy. Both of these intracutaneous skin tests for pregnancy were at first highly praised by their proposers, but neither could be considered of much value in view of further reports by other investigators (Weisman, A. I., and Yerbury, C. C.: M. Rec. 145: 203, 1937. Schwartz, E.: Am. J. Surg. 33: 225, 1936. Schneider, B., and Cohen, A.: J. A. M. A. 109: 115, 1937. Gill, A. M., and Howkins, J.: Brit. M. J. 2: 1069, 1937. Weisman, A. I.: Am. J. Obst. & Gynec. 35: 354, 1938. Gersh, I.: Am. J. Obst. & Gynec. 35: 301, 1938. Frank, C. W., and Wahrsinger, P. B.: Am. J. Obst. & Gynec. 35: 303, 1938. Lass, P. M., Enderle, E. S., and Kurzrok, R.: Endocrinology 23: 71, 1938. Hoffmann, P. E., and Fough, F. L.: Am. J. Obst. & Gynec. 35: 680, 1938. Graffagnino,

P., and von Hamm, E.: South. M. J. 31: 169, 1938. Friedman, J. J., and Fink, H.: Am. J. Obst. & Gynec. 36: 116, 1938. Parsons, S. R.: Surg., Gynec. & Obst. 68: 187, 1939. Hadley, H. G.: Am. J. Obst. & Gynec. 39: 894, 1940. Mandy, T. E., and Mandy, A. J.: Am. J. Obst. & Gynec. 41: 109, 1941).

In conclusion, it may be stated that we were unable to duplicate or confirm the excellent results obtained with this test by Falls, Freda, and Cohen. Our figures indicate a gross inaccuracy of over 29 per cent in 150 such tests. We agree with Falls and his colleagues in their statement, referring to the other skin tests for pregnancy, that owing to the high percentage of false reactions the use of these procedures for diagnostic purposes is useless.

However, since no one group of investigators can lay claim to being the "last word" in scientific research, we herewith have submitted our findings and look forward to the future reports on the subject.

Abner I. Weisman, M.D.
Arnold F. Snyder, M.D.

New York, N. Y.

The above letter was submitted to Dr. Falls for his comment. He states in his reply that the test under consideration has continued to give him good results and that favorable results on its employment have been reported by Dr. Raymond E. Watkins, of Portland, Ore., Dr. Russell W. Alles, of Detroit, Mich., Dr. William T. Pride, of Memphis, Tenn. (94 per cent correct), and Dr. Arthur Bill, of Cleveland, Ohio. Dr. Falls also states that at the Cook County Hospital, 30 out of 36 potential ectopic pregnancies have been diagnosed correctly by this method. He has had no other communications indicating a degree of failure such as that reported by the writers of the foregoing letter.

Additional Report on a Case of Cerebellar Cyst Complicating Pregnancy

To the Editor:

In the September, 1937, issue of The American Journal of Obstetrics and Gynecology, I reported a case of Angiomatosis Retinae (von Hippel's disease, Lindau's disease) Complicated by Pregnancy. This case was reported because of the extreme rarity of the condition. It appeared to be the second case recorded in the literature in which pregnancy was noted as a complication, and was the first for which cesarean section was performed with angiomatosis retinae as the sole indication.

Angiomatosis retinae is a disease characterized by immense dilatation and tortuosity of retinal vessels, and the development of angiomas usually toward the peripheral retina (von Hippel's disease). It is frequently associated with angiomatous cysts of the brain and spinal cord, and malformations or cysts of various somatic organs. When this association is present the condition is known as Lindau's disease.

As a result of ophthalmologic consultation with Dr. John N. Evans, cesarean section under local anesthesia was deemed advisable. It was felt that the already dilated and diseased vessels might not withstand the marked vascular strain that inevitably accompanies spontaneous labor. The fact that there might be an associated lesion elsewhere in the central nervous system or in one of the parenchymatous organs was also considered.

On April 9, 1936, a classical section was performed under local anesthesia, and the patient was delivered of a normal, living, male infant, weighing 2,940 Gm. Sterilization was recommended, but consent was refused by the husband. The postoperative course was uneventful and the patient was discharged from the hospital on April 26, 1936, seventeen days after the operation.

In summarizing this case report, the following statement was made:

"While, up to the present time, there is no definite evidence of an associated Lindau's syndrome in this patient, cases of this type should be followed by both x-ray and physical examination for evidence of pathology in the central nervous system or somatic organs."

On April 26, 1941, this patient was admitted to the Neuro-Surgical Service of the Brooklyn Hospital complaining of nausea and vomiting, increasingly severe headaches, and inability to get about because of unsteadiness of gait. A diagnosis of cerebellar tumor was made and on April 28, 1941, a posterior fossa craniotomy was performed.

In the left cerebellar lobe there was encountered a cyst containing approximately 30 to 40 c.c. of xanthochromic fluid. The cyst was evacuated, but no attempt was made to remove the cyst wall. The postoperative diagnosis was left cerebellar cyst, the postoperative course was uneventful, and the patient was discharged from the hospital on May 27, 1941. The discharge diagnosis: Angiomatosis retinae (von Hippel's disease) cerebellar cyst, left side (Lindau's disease).

MERVYN V. ARMSTRONG, M.D.

85 PIERREPONT STREET,
BROOKLYN, N. Y.

Items

American Board of Obstetrics and Gynecology

The written examination and review of case histories (Part I) for Group B candidates will be held in the various cities of the United States and Canada on Saturday, January 3, 1942, at 2:00 P.M. Formal notice of the place of examination will be sent each candidate several weeks in advance of the examination date. No candidate will be admitted to examination whose examination fee has not been paid at the Secretary's Office. Candidates who successfully complete the Part I examination will proceed automatically to the Part II examination held in June, 1942.

Candidates for *reexamination* in Part I (written paper and submission of case histories) must request such reexamination by writing the Secretary's Office not later than November 15, 1941. Candidates who are required to take reexaminations must do so before the expiration of three years from the date of their original examination.

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting at Atlantic City, N. J., in June, 1942, immediately prior to the annual meeting of the American Medical Association.

Application for admission to Group A, Part II, examinations must be on file in the Secretary's Office not later than March 1, 1942.

As previously announced in the Board booklet, this fiscal year (1941-1942) of the Board marks the close of the two groups of classification of applicants for examination. Thereafter, the Board will have only one classification of candidates, and all will be required to take the Part I examinations.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

Fellowship in Public Health Obstetrics

The Alabama State Department of Public Health, in cooperation with the Children's Bureau of the United States Department of Labor, announces fellowships in public health obstetrics for physicians who have had a minimum of a year's rotating internship and one year of obstetric training. Training provided will embrace field work in already established maternity clinics in rural areas; in the organization of new centers and rotating through the various departments and projects connected with the obstetric aspects of public health. A stipend of $150.00 a month plus travel while in the field is provided. Applications should be sent to Dr. J. N. Baker, State Health Officer, Montgomery, Alabama.

Books Received

THE AMERICAN ILLUSTRATED MEDICAL DICTIONARY. By W. A. Newman Dorland, M.D., F.A.C.S. Nineteenth edition, revised and enlarged, with 914 illustrations, including 269 portraits. 1647 pages. W. B. Saunders Company, Philadelphia, 1941.

GENITAL FUNCTIONS AND THEIR HORMONAL REGULATIONS. Clinical and Experimental Investigations. By Bernhard Zondek. Illustrated, 264 pages. The Williams & Wilkins Company, Baltimore, 1941.

COMMUNITY ORGANIZATION FOR HEALTH EDUCATION. A Committee Report of the American Public Health Association. 120 pages. The Technology Press, Cambridge, Mass., 1941.

ABDOMINAL SURGERY OF INFANCY AND CHILDHOOD. By William E. Ladd, Professor of Child Surgery at Harvard Medical School, etc., and Robert E. Gross, Associate in Surgery, Harvard Medical School, etc. 268 illustrations, 455 pages. W. B. Saunders Company, Philadelphia, 1941.

ENDOCRINOLOGY. By R. G. Hoskins, Ph.D., M.D., Director of Research, the Memorial Foundation for Neuro-Endocrine Research, Harvard Medical School. Illustrated, 388 pages. W. W. Norton & Company, New York, 1941.

TUBERCULOSIS Y PSICOPATIAS. By Dr. Ramon Melgar. 266 pages. Talleres Graficos "Gasperini," Buenos Aires.

BIOLOGICAL SYMPOSIA. Vol. III. Muscle. Edited by Wallace O. Fenn, Professor of Physiology, School of Medicine, University of Rochester, N. Y. Illustrated, 370 pages. The Jaques Cattell Press, Lancaster, Pa., 1941.

RADIATION THERAPY. Its Biologic Fundamentals. By Friedrich Ellinger, M.D., Research Fellow, Radiotherapy Department, Montefiore Hospital, New York City. 79 figures in text, 360 pages. Nordemann Publishing Company, Inc., New York, 1941.

OBSTETRICS FOR NURSES. By Joseph B. DeLee, M.D., Professor of Obstetrics and Gynecology, Emeritus, University of Chicago, etc., and Mabel C. Carmon, R.N., Chief Supervisor and Instructor in the Birth Rooms, Chicago Lying-In Hospital, etc. Twelfth edition, revised. 291 figures, 651 pages. W. B. Saunders Company, Philadelphia, 1941.

THE PREMATURE INFANT. Its Medical and Nursing Care. By Julius H. Hess, M.D., Professor and Head of Department of Pediatrics, University of Illinois College of Medicine, etc., and Evelyn C. Lundeen, R.N., Supervisor, Premature Infant Station, Sarah Morris Hospital, Chicago. 309 pages, 74 illustrations. J. B. Lippincott Company, Philadelphia, 1941.

OPERATIVE SURGERY, Including Anesthesia, Pre- and Postoperative Treatment, Surgical Technic, Blood Transfusion and Abdominal Surgery. Edited by Frederic W. Bancroft, M.D., F.A.C.S., Associate Clinical Professor of Surgery, Columbia University, etc. 1102 pages, illustrated. D. Appleton-Century Co., New York, 1941.

COMPLETE WEIGHT REDUCER. By C. J. Gerling. Harvest House, New York, 1941.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

American Gynecological Society. *President,* W. C. Danforth, Evanston, Ill. *Secretary,* H. C. Taylor, Jr., 830 Park Ave., New York, N. Y. Next meeting, May, 1942, Sky Top, Pa.

American Association of Obstetricians, Gynecologists and Abdominal Surgeons. *President,* W. R. Cooke, Galveston, Texas. *Secretary,* James R. Bloss, 418 11th Street, Huntington, W. Va. Annual meeting will be held at White Sulphur Springs, Va., September 9-11, 1942.

Central Association of Obstetricians and Gynecologists. *President,* Thomas B. Sellers, New Orleans, La. *Secretary-Treasurer,* W. F. Mengert, Iowa City, Iowa. Next meeting, New Orleans, La., Fall of 1941.

South Atlantic Association of Obstetricians and Gynecologists. *President,* R. A. Bartholomew, Atlanta, Ga. *Secretary,* Robert A. Ross, Durham, N. C. Next meeting, February 6-7, 1942, Atlanta, Ga.

A. M. A. Section on Obstetrics and Gynecology. *Chairman,* W. T. Dannreuther. *Secretary,* Philip F. Williams, 2206 Locust St., Philadelphia, Pa. Next meeting, June, 1942, Atlantic City, N. J.

New York Obstetrical Society. *President,* H. J. Stander. *Secretary,* Ralph A. Hurd, 37 E. 64th Street, New York City. Second Tuesday, from October to May, Yale Club.

Obstetrical Society of Philadelphia. *President,* T. L. Montgomery. *Secretary,* John C. Hirst, 500 North 20th St., Philadelphia, Pa. First Thursday, from October to May.

Chicago Gynecological Society. *President,* Charles E. Galloway. *Secretary,* James A. Gough, 104 S. Michigan Ave., Chicago, Ill. Third Friday, from October to June, Hotel Knickerbocker.

Brooklyn Gynecological Society. *President,* George G. Cochran. *Secretary,* John J. Madden, 362 Washington, Ave., Brooklyn N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Avenue, Brooklyn, N. Y.

Baltimore Obstetrical and Gynecological Society. *President,* Abraham Samuels, *Secretary-Treasurer,* Frank K. Morris, 11 East Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Building.

Cincinnati Obstetrical Society. *President,* E. W. Enz. *Secretary,* Edward Friedman, 19 West Seventh St., Cincinnati, O. Third Thursday of each month.

Louisville Obstetrical and Gynecological Society. *President,* Layman A. Gray. *Secretary,* E. P. Solomon, Hegburn Building, Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.

Portland Society of Obstetrics and Gynecology. *President,* Howard Stearns. *Secretary,* William M. Wilson, 545 Medical Arts Bldg., Portland, Ore. Last Wednesday of each month.

Pittsburgh Obstetrical and Gynecological Society. *President,* Thomas Evans, Jr. *Secretary,* Joseph A. Hepp, 121 University Place, Pittsburgh, Pa. First Monday of October, December, February, April, and June.

Obstetrical Society of Boston. *President,* John Rock. *Secretary,* Judson A. Smith, 264 Beacon St., Boston, Mass. Third Tuesday, October to March, Harvard Club.

New England Obstetrical and Gynecological Society. *President,* Frederick L. Good. *Secretary,* R. J. Heffernan, 475 Commonwealth Avenue, Boston, Mass. Meetings held in May and December.

Pacific Coast Obstetrical and Gynecological Society. *President,* John Vruwink. *President-Elect,* T. Floyd Bell. *Secretary-Treasurer,* William Benbow Thompson, 6253 Hollywood Boulevard, Los Angeles, Calif. Next meeting, Los Angeles, Calif., November 5 to 8, 1941.

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*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL.

Washington Gynecological Society. *President,* R. L. Sylvester. *Secretary,* W. R. Thomas, 1830 K. Street, N. W., Washington, D. C. Fourth Saturday, October to May.

New Orleans Obstetrical and Gynecological Society. *President,* E. L. Zander. *Secretary,* Eugene Countiss, 921 Canal St., New Orleans, La. Meetings held every other month.

St. Louis Gynecological Society. *President,* E. Lee Dorsett. *Secretary,* Joseph A. Hardy, Jr., 4952 Maryland Ave., St. Louis, Mo. Second Thursday, October, December, February, and April.

San Francisco Gynecological Society. *President,* T. Henshaw Kelly. *Secretary,* R. Glenn Craig, 490 Post Street, San Francisco, Calif. Regular meetings held second Friday in month, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.

Texas Association of Obstetricians and Gynecologists. *President,* Roy Grogan. *Secretary,* J. McIver, 714 Medical Arts Building, Dallas, Texas. Next meeting, Galveston, Texas, September, 1941.

Michigan Society of Obstetricians and Gynecologists (formerly the Detroit Obstetrical and Gynecological Society). *President,* H. C. Walser. *Secretary,* Harold C. Mack, 955 Fischer Bldg., Detroit, Mich. Meeting first Tuesday of each month from October to May (inclusive).

Obstetric Society of Syracuse Hospitals. *President,* Francis R. Irving. *Secretary,* Nathan N. Cohen, 713 East Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.

Alabama Association of Obstetricians and Gynecologists. *President,* T. M. Boulware, Birmingham, Ala. *Secretary,* John Newdorp, Montgomery, Ala. Next meeting Montgomery, Ala., April, 1942.

San Antonio Obstetric Society. *President,* I. T. Cutter. *Secretary,* S. Foster Moore, Jr., San Antonio, Texas. Meetings held first Tuesday of each month at Gunter Hotel.

Erratum

In the article by U. J. Salmon et al., on "The Treatment of Abnormal Uterine Bleeding With Androgens," in the June, 1941, issue, page 1002, the heading, "value of methyl testosterone" should read "value of ethinyl testosterone." Attention is called likewise to errors in the list of references, pages 1008 and 1009, which correctly are as follows: (22) J. Clin. Endocrinol. **1**: 554, 1941; (35) J. Clin. Endocrinol. **1**: 62, 1941; and (69) J. Clin. Endocrinol. In press.